NON-CONFIDENTIAL

Dkt No. 6680.008

OTD DISCLOSURE NO: OUHSC030 DATE RECEIVED OTD: 3/9/01

UNIVERSITY OF OKLAHOMA
PROPRIETARY INFORMATION/INVENTION DISCLOSURE

NOTE: This statement shall be treated as confidential information except for specific sections as noted. Except for individuals engaged in the evaluation and approval process, the information will not be divulged to others without proper confidentiality agreements in place, except as required by law. The objective of the form is to obtain the information necessary to determine whether to pursue patent protection for your invention.

SECTION I
NONCONFIDENTIAL INFORMATION

1. **Nonconfidential title of the work:**
   Soluble HLA Ligand Database and Epitope Prediction Software

2. **Nonconfidential lay abstract of invention:**
   The present invention envisions the generation of a sequence database resulting from endogenously produced and loaded ligands identified to be bound to sHLA molecules. Epitope Prediction software would then utilize the resultant ligand database to predict viral, bacterial, tumor, or human protein sequences for ligands likely to bind a particular HLA class I or class II protein.

3. **Nature of work:** Machine ☐ Process ☐ Utility ☐ Software ☒

   If Software: Have proper copyright markings been utilized? Yes ☐ No ☐

OFFICE OF TECHNOLOGY DEVELOPMENT
University of Oklahoma Health Sciences Center
1000 Stanton L.Young, Room 121

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OFFICE OF TECHNOLOGY DEVELOPMENT
University of Oklahoma Health Sciences Center
1000 Stanton L.Young, Room 121
Oklahoma City, OK 73117-1213
Telephone (405) 271-2090
Fax (405) 271-8651

CONFIDENTIAL

4. Please list all submitters below:

Submitters	Office Mailing Address	% of Contribution*	Office Phone No.	Citizenship
a. William H. Hildebrand	OUHSC 975 NE 10th Street, BRC 317 Oklahoma City, OK 73104	85	(405) 271-1203	US
b. Kiley R.Prilliman	8284 Flanders Drive #57 San Diego, CA 92126	15	(858)678-4552	US
c.			( )	
d.			( )	
e.			( )	

*NOTE: This % of contribution is an estimate providing for the division of proceeds, and not an assessment of legal inventorship. If this column is blank, submitters will share equally any revenues generated based on information contained in this disclosure.

5. If you have any other affiliations (i.e. received salary from another party, housed in other facilities besides university facilities), please list below:

Submitters	Other Affiliations	% of Salary Other Affiliation Paid
a. William H. Hildebrand	Pure Protein, L.L.C. Consultant	0
b. Kiley R. Prilliman	LaHoya Institute of Allergy and Immunology	100
c.		
d.		
e.		

6. Has a Conflict of Interest form been filed with the Provost's office? Yes ☒ No ☐

7. List specific University research support as well as external funding. List all sources, including matching funds.

a. Name of sponsoring agency, company, or internal funding
The technology described here was licensed to Pure Protein, L.L.C. The Licensing Agreement was filed between OU and Pure Protein, L.L.C. 6/3/99. Work for this technology was supported through both Sponsored Research Agreements (ORA#20000017 and ORA#20010109) between OU and Pure Protein, L.L.C and NIH Contract#NO1-AI-95360

b. Principal Investigator
William H. Hildebrand

c. Co-Investigators; Consultants

d. Grant or Project Number
OU-Pure Protein, L.L.C. Sponsored Research Agreements ORA#20000017, ORA#20010109 and NIH Contract#NO1-AI-95360.

University of Oklahoma Health Sciences Center

INVENTION DISCLOSURE

Please be as accurate and thorough as possible in supplying the information requested. For all requested dates, list month, day and year. When completed, the form should be delivered to the Office of Research Administration, LIB-121.

1. Title of Invention: HLA class I sequence based typing

Full Name of Inventor: William Henry Hildebrand Citizen of: USA
Residence Address: 900 Northcreek Drive, Edmond, OK 73034
Supervisor: Richard M. Hyde

Full Name of Inventor: Mary Ellexson Citizen of: USA
Residence Address: 803 East Drive Apt. B, Oklahoma City, OK 73105
Supervisor: William Hildebrand

Full Name of Inventor: Pierre Chretien Citizen of: Canada
Residence Address: 7793 Rue De Gaspe Montral, Quebec ~~H2R2A5~~ H2R 2A5
Supervisor: David Lorenz

Full Name of Inventor: R. Scott Duthie Citizen of: USA
Residence Address: 2767 S. Lieberger Terrace Milwaukee, WI 53207
Supervisor: Karen Foster

Full Name of Inventor: Citizen of:
Residence Address:
Supervisor:

If more space is needed to list inventors, please add additional sheets giving the above information.

2. Invention disclosed or described in Lab Notebook(s) No. 5, Page(s) 4-33.

3. a. The invention was first conceived or thought of in a workable form on 10/24/96 (date).
   b. The invention was first disclosed to others on Not disclosed.
   c. The person(s) to whom the invention was first disclosed are ABOVE.
   d. The first written description of the invention is in the form of NMDP REQ dated 12/4/96 and is now located ORA.
   e. The first sketch or drawing of the invention was made on 12/4/96. and is now located BMSB 1013
   f. The first construction of the invention was begun on _____ and finished on 12/4/96.
   g. The invention was first successfully tested on 11/26/96 and the test results are now located BMSB 1038.

have attempted to solve the problem. Point out disadvantages and weaknesses in prior art. Include literature references and copies where available.

c. Description of invention, including a specific embodiment. Point out important features and points believed to be novel. State advantages of invention and sacrifices, if any, made to achieve these advantages. Describe any experiments conducted and the results of those experiments.

d. Is the concept of the invention applicable to other problems and fields of interest? If so, what are they and how would the principles of the invention be used?

e. What commercial products(s) might result from this invention? Who would purchase the product(s)? What is the potential annual market value of the product(s) (please justify your market estimate as best you can)?

8. The invention described by the attached patent disclosure is submitted pursuant to my Employment Agreement with the University of Oklahoma Health Sciences Center:

Inventor(s) _____ Date 12-10-96
Signature

William H. Hildebrand
Printed Name

_____ Date 12/11/96
Signature

Pierre Chretien
Printed Name

_____ Date 12/10/96
Signature

Mary Ellexson
Printed Name

_____ Date 12/12/96
Signature

_____
Printed Name

_____ Date _____
Signature

_____
Printed Name

Contact person for more data: _____ Telephone #: _____

Mailing Address: _____

For Office of Research Administration use only:

Date Received: 12/13/96 Docket #: _____

FFN: Yes_____ No ✓

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OTD DISCLOSURE NO: 01 HSC 032 DATE RECEIVED OTD: 3/9/01

1524003-01-0004

UNIVERSITY OF OKLAHOMA
PROPRIETARY INFORMATION/INVENTION DISCLOSURE

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SECTION I
NONCONFIDENTIAL INFORMATION

1. Nonconfidential title of the work:

   Using sHLA molecules for Epitope Discovery

2. Nonconfidential lay abstract of invention:

   The present invention envisions a method of comparative ligand mapping from MHC Class I positive cells. This invention uses a direct approach for identifying ligands unique to infected cells, tumor cells, or cell transfected/infected with a gene of interest and utilizes a subtractive comparison of peptide ligand maps from transfected/infected and uninfected cells. Ligands unique to transfected/infected, tumor cells can then be sequenced and subsequently tested in functional assays.

3. Nature of work: Machine ☐ Process ☒ Utility ☐ Software ☐

   If Software: Have proper copyright markings been utilized? Yes ☐ No ☐

CONFIDENTIAL

4. Please list all submitters below:

Submitters	Office Mailing Address	% of Contribution*	Office Phone No.	Citizenship
a. William H. Hildebrand	OUHSC 975 NE 10th Street, BRC 317 Oklahoma City, OK 73104	75	(405) 271-1203	US
b. Heather D. Hickman	OUHSC 975 NE 10th Street, BRC 317 Oklahoma City, OK 73104	25	(405) 271-1203	US
c.			( )	
d.			( )	
e.			( )	

*NOTE: This % of contribution is an estimate providing for the division of proceeds, and not an assessment of legal inventorship. If this column is blank, submitters will share equally any revenues generated based on information contained in this disclosure.

5. If you have any other affiliations (i.e. received salary from another party, housed in other facilities besides university facilities), please list below:

Submitters	Other Affiliations	% of Salary Other Affiliation Paid
a. William H. Hildebrand	Pure Protein, L.L.C. Consultant	0
b. Heather D. Hickman	none	0
c.		
d.		
e.		

6. Has a Conflict of Interest form been filed with the Provost's office? Yes ☒ No ☐

7. List specific University research support as well as external funding. List all sources, including matching funds.

a. Name of sponsoring agency, company, or internal funding
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b. Principal Investigator
William H. Hildebrand

c. Co-Investigators; Consultants

d. Grant or Project Number
OU-Pure Protein, L.L.C. Sponsored Research Agreements ORA#20000017, ORA#20010109 and NIH Contract#NO1-AI-95360.

CONFIDENTIAL

e. **University Account Code**
C7000901, C7000902, and C2164201

f. **Attach copy of Grant or Contract Document.**

CONFIDENTIAL

Has a biological, chemical or physical material or substance obtained from others been used in the creation of this invention? Yes ☒ No ☐

If Yes, was a Materials Transfer Agreement or similar document used to obtain the material or substance? Yes ☒ No ☐ See DoD Grant#N00014-95-1-0074 and the NMDP c ntract with the University of OK Health Sciences Center.

If Yes, attach a copy of the agreement.

If No, identify source and explain.

GENERAL PATENT INFORMATION

In order to obtain patent protection, your invention must demonstrate the following:

1. New (or novel): The invention must be new, that is, it has not been previously used, sold or described publicly.

2. Useful: The invention must have an actual use and not be just a subject for additional research.

3. Non-obvious: The invention must not be obvious at the time of conception to another person having ordinary skill in the art.

The patent laws set forth those classes of inventions eligible for patenting as follows:

1. Machines

2. Processes

3. Compositions of Matter

4. Manufacture

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SECTION II
PROPRIETARY INFORMATION
DOCUMENTATION

OBJECTIVE: To define the nature, purpose and operation of the invention, a practical presentation is preferable to highly theoretical material.

EVENTS	DATE	SUPPORTING DOCUMENTATION
1. Initial Idea	1/23/98	See attached grant proposal.
2. First oral or written description of information. (Please provide copy of witnessed lab notebook showing date of discovery.)	1/23/98	See attached grant proposal. See Laboratory Notebook: Heather Hickman Book #5, pp20 through current notebook. See NIH contract NO1-AI-95360. See attached manuscript.
3. Level of testing completed (Lab scale, prototype, etc.)	8/29/98	See Laboratory Notebook: Heather Hickman Book #5, pp20 through current notebook. See attached manuscript.
4. Prototype completed	5/1/00	See Laboratory Notebook: Heather Hickman Book #5, pp20 through current notebook. See attached manuscript.
5. First written or oral publication date (include date of printed abstracts, any oral presentations, or electronic publication dates of journals, poster presentations, presentations to industry etc.) Attach copies.	7/7/00	See attached manuscript.
6. Other external oral or written disclosures.	10/10/00	Patent Application filed by Dunlap, Codding, & Rogers, P.C. 10/10/00, Docket#6680.001, Patent Application 60/240,143.

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7. Provide a full description of the proprietary information. This information should be in such detail as to "teach" the invention and to provide the basis for a patent application. Someone skilled in the art should be able to reproduce the invention within a reasonable period of time based n the information supplied here.

   a. Complete detailed description of invention (attach separate sheets if necessary):

      See Attached Manuscript

   b. Provide a complete description of the State of the Art prior to your invention. Include a list of any literature references, patent applications, or issued patents you are aware of. Cite source of literature or patent search information. (Attach separate sheets if necessary.)

      See Attached Manuscript.

   c. Describe the advantages, improvements and technical impact of your invention over existing practice (novel or unusual features):

      See Attached Manuscript.

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d. List the areas of applications of invention indicating the problem s lved in the area by your invention:

See Attached Manuscript.

e. List the main advantages of the invention (list in the order as the advantages would relate to the list of applications in item d. above):

See Attached Manuscript.

f. List any known disadvantages using the same format as above:

See Attached Manuscript.

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8. Describe the state of development of your invention? Is there a prototype or samples of materials available for viewing or testing? Include any test results available.

Yes. See attached manuscript and Laboratory Notebook(s): Heather Hickman book #5, pp20 through present day notebook.

9. Outline the further research and development, if any, that would greatly enhance the state of development of the invention.

See Attached Manuscript.

10. List any funded or submitted proposals that have been submitted previously based on this invention. Were proprietary markings affixed to the proposal?

11. Attach any pertinent tables or drawings describing the invention.

12. Provide any other comments you may have regarding your proprietary information.

13. Provide the date and description of all planned publications, oral presentations, poster sessions, abstracts, preprints, or other public dissemination of the invention. (Check to see if the journal publishes electronically and provide OTD with the earliest of the dates.)

DATE	DESCRIPTION
Unknown	Unknown

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14. Submitter's signatures (this disclosure is submitted under the University of Oklahoma Intellectual Property Policy, Patents, Paragraph 1.1.)

In consideration of employment or a consulting relationship, and subject to any prior agreements with The University of Oklahoma Board of Regents, this invention/discovery is hereby assigned to The University of Oklahoma Board of Regents, together with all patents covering said invention/discovery.

Signature	Date	Home Address / City, State, Zip
[signature]	3-9-01	900 Northcreek Drive Edmond, OK 73034
Heather O Hackman	03/09/01	7901 N 120th Ave. Owasso, OK 74055

15. Invention Disclosed to and Understood By (Witness):

Signature _____ Date _____

16. Office of Technology Development

Signature _____ Date _____

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SECTION III
COMMERCIAL POTENTIAL

NOTE: The information contained in this section will not be distributed to anyone outside of the University of Oklahoma, except as required by law.

1. Where would your idea have commercial value?

U.S.	☒	South America	☐	Africa	☐	
Canada	☐	Japan	☐	Australia	☐	
Europe	☐	Asia	☐	Other	☒	PCT countries to be determined.

2. In your judgment, does the proprietary information require copyright or patent protection in order to be successfully marketed:

a. Patent protection ☒
b. Copyright protection ☒
c. Know-How could be licensed ☒

3. List any companies, and individuals within those companies, that you feel may have a commercial interest in licensing the invention. (Indicate by special note those companies that have contacted you regarding the invention.)

The technology described here was licensed to Pure Protein, L.L.C. The Licensing Agreement was filed between OU and Pure Protein, L.L.C. 6/3/99. Work for this technology was supported through both Sponsored Research Agreements (ORA#20000017 and ORA#20010109) between OU and Pure Protein, L.L.C and NIH Contract#NO1-AI-95360.

A Patent Application for this technology has been filed by the law offices of Dunlap, Codding, & Rogers, P.C. 10/10/00, Docket#6680.001, Patent Application 60/240,143.

University of Oklahoma Health Sciences Center
Office of Research Administration

ROUTING FORM

(above bold line for ORA use only).

Date Received: 1-23-98/3:50
Received by: LH

ORA# 980340

1. Principal Investigat r	2. Social Security Number	3. % Time	4. Sponsor Deadline
Dr. William Hildebrand	344-56-8021	15	02/02/98

5. College/Department	6. Campus Address	7. Phone	8. E-mail address
Microbiology & Immunology	975 NE 10th BRC Rm 317	405-271-1203 Fax 271-3874	william-hildebran@ouhsc.edu

9. University Center: If an OUHSC approved Center should receive 10% IDC recovery, list the Center's name. If the project is being administered through the Center rather than an academic department, recovery will be at 18% and approvals listed below are required.

Center:

Department Chair: Center Administrative Head:

10. Co-investigators: My initials below confirm my review of this application and my adherence to the certifications located on the reverse side of this page.

Name	SSN	%Time	College/Dept	Init: Co-Inves	Chair/Head	Dean
Kennedy	042-52-1503	5%	Micro.& Immunology	BK		

11. Project Title	12. Project Site(s) (Building/Room)
Class I Ligand Diversity	BRC/Rm 317

13. Funding Source/External Sponsor	Sponsor Code (ORA Use Only)
National Institute of Health	

14. Program Announcement/RFA/RFP (No. and Title), if applicable	IDC Rate (ORA Use Only)
PA-97-101, Basic Mechanism of Vaccine Efficacy	

15. Program Type	16.Submission Type
☒ Research ☐ Training/Education	☒ New ☐ Continuation ☐ Competing Renewal ☐ Revision ☐ Other

17. Initial Project Period	18. Direct Costs	19. Indirect Costs	20. Total Costs
12/01/98 thru 11/31/99	223,551	68,563	292,114
21. T tal Period (Not required for non-competing continuations)	**22. Direct Costs**	**23. Indirect Costs**	**24. Total Costs**
12/01/98 thru 11/31/03	876,606	364,012	1,240,618

25. Special Reviews - Project Involves:

☐ Human: Subjects IRB No. ____ ☐ Legend Drugs/Controlled Substances ☐ Institutional Match

☐ Animal: IACUC No: ____ ☐ Biohazards Specify: ____ ☐ Proposal Contains

☑ Recombinant DNA Approval No.: 1104 ☐ Additional Space/Alterations Required Confidential Info on pp: ____

☐ Radioisotopes Minilicense No.: ____ ☐ Req'd Cost Share ☐ College/Dept. Match

(8) 1-28-98/lh

25. Does th project utilize patients, personnel r facilities at any of the following? (Check all that apply and obtain approval signature here or on supporting document.)

- ☐ The University Hospital (TUH) — Signature: _____
- ☐ Children's Hospital (CHO) — Signature: _____
- ☐ Oklahoma Medical Research Foundation (OMRF) — Signature: _____
- ☐ Veteran's Administration (DVAMC) — Signature: _____
- ☐ Dean A. McGee Eye Institute (DMEI) — Signature: _____
- ☐ Columbia Presbyterian Hospital (PH) — Signature: _____
- ☐ University of Oklahoma, Norman (OU-Norman) — Signature: _____
- ☐ Other (Specify) _____ — Signature: _____

27. Certifications, Disclosures and Assurances

The proposed project or relationship with this Sponsor does/does not (*see signature box below) present a potential conflict of interest or the appearance of a conflict of interest for investigators involved in this project; if answered in the affirmative, then all investigators so involved have provided a complete disclosure of this matter to the appropriate University official as required by the Policy Regarding Conflicts of Interest.

The proposal submitted herewith is (i) complete in its technical content (ii) adheres to the rules of proper scholarship, including specifically the proper attribution and citation for all text and graphics, and (iii) complies with sponsor and university standards for the integrity of research.

If this proposal is funded and accepted by the University, I will conduct the project in accordance with the terms and conditions of the sponsoring agency and the policies of the University, and I will be fully responsible for meeting the requirements of the award, including submitting all required technical reports and deliverables on a timely basis, and properly disclosing all inventions to the University's Office of Research Administration, in accordance with sponsor and university policy.

For federal applications in accordance with federal requirements, I certify that (1) I am not delinquent on any federal debt; (2) I am not presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from current transactions by any federal department or agency; (3) no federal appropriated funds have been or will be paid to influence or attempt to influence the granting of this award; and (4) I am not delinquent in submitting final project reports to sponsors for previous awards I have received.

REQUIRED SIGNATURES		Additional Signatures (when required by ORA)	
28. Principal Investigator *This Proposal ☐ does ☑ does not represent a conflict of interest as described above.	Date 1-23-98	Legal Counsel	Date
29. Department Chair	Date 1-23-98	Development Office	Date
30. College Dean	Date 1-23-98	Office of Grants and Contracts Administration	Date
31. Research Administration	Date 1/27/98	Other	Date

32. Comments/Special Instructions

AA

Form Approved Through 8/30/87
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

Grant Applicati n

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

LEAVE BLANK—FOR PHS USE ONLY.		
Type	Activity	Number
Review Group	Formerly	
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT (Do not exceed 56 characters, including spaces and punctuation.)
Class I Ligand Diversity

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES (If "Yes," state number and title)
Number: PA-97-101 Title: Basic Mechanism of Vaccine Efficacy

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME (Last, first, middle)	3b. DEGREE(S)	3c. SOCIAL SECURITY NO.
Hildebrand, William, Henry	Ph.D	344-56-8021

3d. POSITION TITLE
Assistant Professor

3e. MAILING ADDRESS (Street, city, state, zip code)
University of Oklahoma
Health Sciences Center
Dept. of Micro. & Immunology
P.O. Box 26901
Oklahoma City, OK 73190

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Dept. of Micro.&Immunology

3g. MAJOR SUBDIVISION
Immunology

3h. TELEPHONE AND FAX (Area code, number and extension)
TEL: 405-271-1203
FAX: 405-271-3117

E-MAIL ADDRESS:
william-hildebrand@ouhsc.edu

4. HUMAN SUBJECTS	4a. If "Yes," Exemption no. or IRB approval date	Full IRB or Expedited Review	4b. Assurance of compliance no.	5. VERTEBRATE ANIMALS	5a. If "Yes," IACUC approval date	6b. Animal welfare assurance no.
☒ No ☐ Yes				☒ No ☐ Yes		

6. DATES OF PROPOSED PERIOD OF SUPPORT (month, day, year—MM/DD/YY)		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
120198	113103	223,551	292,114	876,606	1,240,618

9. APPLICANT ORGANIZATION
Name: University of Oklahoma
Address: Health Sciences Center
Department of Microbiology
975 NE 10th St.
Oklahoma City, OK 73104

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☒ State ☐ Local
Private: → ☐ Private Nonprofit
Forprofit: → ☐ General ☐ Small Business

11. ORGANIZATIONAL COMPONENT CODE: 01

12. ENTITY IDENTIFICATION NUMBER	Congressional District
73-6017987E8	06

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: Larry Henson, Director
Title: Grants & Contracts Admin.
Address: SCB-219
1100 N. Lindsay
Oklahoma City, OK 73104-5499

Telephone: 405-271-2177
FAX: 405-271-2213

E-Mail Address: larry-henson@ouhsc.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Nancy Nisbett, Director
Title: Office of Research Admin.
Address: LIB 121
1000 Stanton L. Young Blvd
Oklahoma City, OK 73117-1213

Phone: 405-271-2090
FAX: 405-271-8651

E-Mail Address: nancy-nisbett@ouhsc.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI / PD NAMED IN 3a. (In ink. "Per" signature not acceptable.) — DATE: 1-23-98

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. (In ink. "Per" signature not acceptable.) — DATE: 1/27/98

OTD DISCLOSURE NO: 01HSC026 DATE RECEIVED OTD: 3-5-01

UNIVERSITY OF OKLAHOMA
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SECTION I
NONCONFIDENTIAL INFORMATION

1. Nonconfidential title of the work:

   HLA Protein Production From Genomic DNA

2. Nonconfidential lay abstract of invention:

   The present invention envisions a method of producing major histocompatibility complex (MHC) molecules, designated HLA class I and HLA class II in humans. The genes for these MHC molecules have been engineered from genomic DNA so that they are secreted from mammalian cells in a bioreactor unit.

3. Nature of work: Machine ☐ Process ☒ Utility ☐ Software ☐

   If Software: Have proper copyright markings been utilized? Yes ☐ No ☐

OFFICE OF TECHNOLOGY DEVELOPMENT

University of Oklahoma Health Sciences Center
1000 Stanton L.Young, Room 121
Oklahoma City, OK 73117-1213
Telephone (405) 271-2090
Fax (405) 271-8651

4. Please list all submitters below:

Submitters	Office Mailing Address	% of Contribution*	Office Phone No.	Citizenship
a. William H. Hildebrand	OUHSC 975 NE 10th Street, BRC 317 Oklahoma City, OK 73104	70	(405) 271-1203	US
b. Sean Turner	Pure Protein, L.L.C. 800 N Research Pkwy, Suite 414 Oklahoma City, OK 73104	20	(405) 271-3838	United Kingdom
c. Angela D. Luis	Pure Protein, L.L.C. 800 N Research Pkwy, Suite 414 Oklahoma City, OK 73104	10	(405) 271-3838	US
d.			( )	
e.			( )	

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b. Sean Turner	Pure Protein, L.L.C.	100
c. Angela D. Luis	Pure Protein, L.L.C.	100
d.		
e.		

6. Has a Conflict of Interest form been filed with the Provost's office? Yes ☒ No ☐

7. List specific University research support as well as external funding. List all sources, including matching funds.

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   b. Principal Investigator
   William H. Hildebrand

   c. Co-Investigators; Consultants

   d. Grant or Project Number
   OU-Pure Protein, L.L.C. Sponsored Research Agreements ORA#20000017 and ORA#20010109

e. University Account Code
C7000901 and C7000902

f. Attach copy of Grant or Contract Document.

Has a biological, chemical or physical material or substance obtained from others been used in the creation of this invention? Yes ☒ No ☐

If Yes, was a Materials Transfer Agreement or similar document used to obtain the material or substance? Yes ☒ No ☐

If Yes, attach a copy of the agreement. See NMDP contract with the University.

If No, identify source and explain.

GENERAL PATENT INFORMATION

In order to obtain patent protection, your invention must demonstrate the following:

1. New (or novel): The invention must be new, that is, it has not been previously used, sold or described publicly.

2. Useful: The invention must have an actual use and not be just a subject for additional research.

3. Non-obvious: The invention must not be obvious at the time of conception to another person having ordinary skill in the art.

The patent laws set forth those classes of inventions eligible for patenting as follows:

1. Machines

2. Processes

3. Compositions of Matter

4. Manufacture

SECTION II
PROPRIETARY INFORMATION
DOCUMENTATION

OBJECTIVE: To define the nature, purpose and operation of the invention, a practical presentation is preferable to highly theoretical material.

EVENTS	DATE	SUPPORTING DOCUMENTATION
1. Initial Idea	10/30/99	See Laboratory Notebook: Sean Turner Book #5, pp 83 through current notebook.
2. First oral or written description of information. (Please provide copy of witnessed lab notebook showing date of discovery.)	10/30/99	See Laboratory Notebook: Sean Turner Book #5 p. 83 through current notebook.
3. Level of testing completed (Lab scale, prototype, etc.)	10/30/99	See Laboratory Notebook: Sean Turner Book #5 pp. 83 through current notebook.
4. Prototype completed	1/31/00	See Laboratory Notebook: Sean Turner Book 9 pp00 through current notebook.
5. First written or oral publication date (include date of printed abstracts, any oral presentations, or electronic publication dates of journals, poster presentations, presentations to industry etc.) Attach copies.	NA	NA
6. Other external oral or written disclosures.	12/18/00	Patent Application filed by Dunlap & Codding 12/18/00, Docket#6680.003, Patent Application 60/256,410.

7. Provide a full description of the proprietary information. This information should be in such detail as to "teach" the invention and to provide the basis for a patent application. Someone skilled in the art should be able to reproduce the invention within a reasonable period of time based on the information supplied here.

   a. Complete detailed description of invention (attach separate sheets if necessary):

      See Attached Summary/HLA Protein Production From Genomic DNA

   b. Provide a complete description of the State of the Art prior to your invention. Include a list of any literature references, patent applications, or issued patents you are aware of. Cite source of literature or patent search information. (Attach separate sheets if necessary.)

      See Attached Summary

   c. Describe the advantages, improvements and technical impact of your invention over existing practice (novel or unusual features):

      See Attached Summary

d. **List the areas of applications of invention indicating the problem solved in the area by your invention:**

See Attached Summary

e. **List the main advantages of the invention (list in the order as the advantages would relate to the list of applications in item d. above):**

See Attached Summary

f. **List any known disadvantages using the same format as above:**

See Attached Summary

8. Describe the state of development of your invention? Is there a prototype or samples of materials available for viewing or testing? Include any test results available.

Yes. See Laboratory Notebook: Sean Turner Book #5 pp.83 through present day notebook.

9. Outline the further research and development, if any, that would greatly enhance the state of development of the invention.

See Attached Summary

10. List any funded or submitted proposals that have been submitted previously based on this invention. Were proprietary markings affixed to the proposal?

11. Attach any pertinent tables or drawings describing the invention.

12. Provide any other comments you may have regarding your proprietary information.

13. Provide the date and description of all planned publications, oral presentations, poster sessions, abstracts, preprints, or other public dissemination of the invention. (Check to see if the journal publishes electronically and provide OTD with the earliest of the dates.)

DATE	DESCRIPTION
Unknown	Unknown

14. Submitter's signatures (this disclosure is submitted under the University of Oklahoma Intell ctual Property Policy, Patents, Paragraph 1.1.)

In consideration of employm nt or a consulting relationship, and subject to any prior agreements with The University of Oklahoma Board of Regents, this invention/discovery is hereby assigned to The University of Oklahoma Board of Regents, together with all patents covering said invention/discovery.

[signature] Signature	3/2/01 Date	900 Northcreek Drive Home Address Edmond, OK 73034 City, State, Zip
[signature] Signature	3/2/01 Date	4095 McDonald Road Home Address Choctaw, OK 73020 City, State, Zip
[signature] Signature	3/2/01 Date	19107 Prospect Ridge Lane Home Address Houston, TX 77094 City, State, Zip
Signature	Date	Home Address City, State, Zip
Signature	Date	Home Address City, State, Zip

15. Invention Disclosed to and Understood By (Witness):

Signature Date

16. Office of Technology Development

[signature] Signature 3/07/01 Date

SECTION III
COMMERCIAL POTENTIAL

NOTE: The information contained in this section will not be distributed to anyone outside of the University of Oklahoma, except as required by law.

1. Where would your idea have commercial value?

U.S.	☒	South America	☐	Africa	☐
Canada	☐	Japan	☐	Australia	☐
Europe	☐	Asia	☐	Other	☒ PCT countries to be determined.

2. In your judgment, does the proprietary information require copyright or patent protection in order to be successfully marketed:

a. Patent protection ☒
b. Copyright protection ☒
c. Know-How could be licensed ☒

3. List any companies, and individuals within those companies, that you feel may have a commercial interest in licensing the invention. (Indicate by special note those companies that have contacted you regarding the invention.)

This technology results from Support Research Agreements between the University of Oklahoma and Pure Protein, L.L.C. (ORA numbers 20000017 and 20010109). Filing dates for these SRAs were June 3, 1999 and Sep 1,2000 respectively.

A Patent Application for this technology has been filed by the law offices of Dunlap and Codding 12/18/00, Docket#6680.003, Patent Application 60/256,410.

HLA PROTEIN PRODUCTION FROM GENOMIC DNA

Before explaining at least one embodiment of the invention in detail by way of exemplary drawings, experimentation, results, and laboratory procedures, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings, experimentation and/or results. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Class I major histocompatibility complex (MHC) molecules, designated HLA class I in humans, bind and display peptide antigens upon the cell surface. The peptides they present are derived from either normal endogenous proteins ("self") or foreign proteins ("nonself"), such as products of malignant transformation or intracellular pathogens such as viruses. In this manner, class I molecules convey information regarding the internal fitness of a cell to immune effector cells including but not limited to $CD8^+$ cytotoxic T lymphocytes (CTLs), which are activated upon interaction with "nonself" peptides and which lyse or kill the cell presenting such "nonself" peptides.

Class II MHC molecules, designated HLA class II in humans, also bind and display peptide antigens upon the cell surface. However, unlike class I MHC molecules which are expressed on virtually all nucleated cells, class II MHC molecules are normally confined to specialized cells, such as B lymphocytes, macrophages, dendritic cells, and other antigen presenting cells which take up foreign antigens from the extracellular fluid via an endocytic pathway. Therefore, the peptides they bind and present are derived from extracellular foreign antigens, such as products of bacteria that multiply outside of cells, wherein such products include protein toxins secreted by the bacteria that have deleterious and even lethal effects on the host. In this manner, class II molecules convey information regarding the fitness of the extracellular space in the vicinity of the cell displaying the class II molecule to immune effector cells including but not limited to $CD4^+$ helper T cells, which

help eliminate such pathogens both by helping B cells make antibodies against microbes as well as toxins produced by such microbes and by activating macrophages to destroy ingested microbes.

Class I and class II HLA molecules exhibit extensive polymorphism, which is generated by systematic recombinatorial and point mutation events; as such, hundreds of different HLA types exist throughout the world's population, resulting in a large immunological diversity among the population. Such extensive HLA diversity in the population results in tissue or organ transplant rejection between individuals as well as differing susceptibilities and/or resistances to infectious diseases. HLA molecules also contribute significantly to autoimmunity and cancer. Because HLA molecules mediate most, if not all, adaptive immune responses, HLA proteins are needed to study transplantation, autoimmunity, and for developing vaccines.

There are several applications in which purified, individual class I and class II MHC proteins would be highly useful. Such applications include using MHC-peptide multimers as immunodiagnostic reagents for disease resistance/autoimmunity; assessing the binding of potentially therapeutic peptides; elution of peptides from MHC molecules to identify vaccine candidates; screening transplant patients for preformed MHC specific antibodies; and removal of anti-HLA antibodies from a patient. Since every individual has different MHC molecules, the testing of numerous individual MHC molecules is a prerequisite for understanding differences in disease susceptibility between individuals. Therefore, purified MHC molecules representative of the hundreds of different HLA types existing throughout the world's population are highly desirable for unraveling disease susceptibilities and resistances and for designing therapeutics.

Currently there is no readily available source of individual HLA molecules. Until now, the quantities of HLA protein available are small and typically consist of a mixture of different HLA molecules. Production of HLA molecules traditionally involves growth and lysis of cells expressing multiple HLA molecules. Ninety percent of the population is heterozygous at each of the HLA loci; codominant expression results in multiple HLA

proteins expressed at each HLA locus. To purify native class I or class II molecules from mammalian cells requires time-consuming and cumbersome purification methods, and since each cell typically expresses multiple surface-bound HLA class I or class II molecules, HLA purification results in a mixture of many different HLA class I or class II molecules. When performing experiments using such a mixture of HLA molecules or performing experiments using a cell having multiple surface-bound HLA molecules, interpretation of results cannot *directly* distinguish between the different HLA molecules, and one cannot be certain that any particular HLA molecule is responsible for a given result. Therefore, a need exists in the art for a method of producing substantial quantities of individual HLA class I or class II molecules so that they can be readily purified and isolated independent of other HLA class I or class II molecules. Such individual HLA molecules, when provided in sufficient quantity and purity, would provide a powerful tool for studying and measuring immune responses.

The present invention envisions a method of producing MHC molecules which are secreted from mammalian cells in a bioreactor unit. Substantial quantities of individual MHC molecules are obtained by modifying class I or class II molecules so they are secreted. Secretion of soluble MHC molecules overcomes the disadvantages and defects of the prior art in relation to the quantity and purity of MHC molecules produced. Problems of quantity are overcome because the cells producing the MHC do not need to be detergent lysed or killed in order to obtain the MHC molecule. In this way the cells producing secreted MHC remain alive and therefore continue to produce MHC. Problems of purity are overcome because the only MHC molecule secreted from the cell is the one that has specifically been constructed to be secreted. Thus, transfection of vectors encoding such secreted MHC molecules into cells which may express endogenous, surface bound MHC provides a method of obtaining a highly concentrated form of the transfected MHC molecule as it is secreted from the cells. Greater purity can be assured by transfecting the secreted MHC molecule into MHC deficient cell lines.

Production of the MHC molecules in a hollow fiber bioreactor unit allows cells to be cultured at a density substantially greater than conventional liquid phase tissue culture

permits. Dense culturing of cells secreting MHC molecules further amplifies the ability to continuously harvest the transfected MHC molecules. Dense bioreactor cultures of MHC secreting cell lines allow for high concentrations of individual MHC proteins to be obtained. Highly concentrated individual MHC proteins provide an advantage in that most downstream protein purification strategies perform better as the concentration of the protein to be purified increases. Thus, the culturing of MHC secreting cells in bioreactors allows for a continuous production of individual MHC proteins in a concentrated form.

The method of the present invention begins by obtaining genomic or complementary DNA which encodes the desired MHC class I or class II molecule. Alleles at the locus which encode the desired MHC molecule are PCR amplified in a locus specific manner. These locus specific PCR products may include the entire coding region of the MHC molecule or a portion thereof. In some cases a nested or hemi-nested PCR is applied to produce a truncated form of the class I or class II gene so that it will be secreted rather than anchored to the cell surface. In other cases the PCR will directly truncate the MHC molecule.

Locus specific PCR products are cloned into a mammalian expression vector and screened with a variety of methods to identify a clone encoding the desired MHC molecule. The cloned MHC molecules are DNA sequenced to insure fidelity of the PCR. Faithful truncated clones of the desired MHC molecule are then transfected into a mammalian cell line. When such cell line is transfected with a vector encoding a recombinant class I molecule, such cell line may either lack endogenous class I expression or express endogenous class I. It is important to note that cells expressing endogenous class I may spontaneously release MHC into solution upon natural cell death. In cases where this small amount of spontaneously released MHC is a concern, the transfected class I MHC molecule can be "tagged" such that it can be specifically purified away from spontaneously released endogenous class I molecules in cells that express class I molecules. For example, a DNA fragment encoding a His tail which will be attached to the protein may be added by the PCR reaction or may be encoded by the vector into which the gDNA fragment is cloned, and such His tail will further aid in purification of the class I molecules away from endogenous class I

molecules. Tags beside a histidine tail have also been demonstrated to work and are logical to those skilled in the art of tagging proteins for downstream purification.

Cloned genomic DNA fragments contain both exons and introns as well as other non-translated regions at the 5′ and 3′ termini of the gene. Following transfection into a cell line which transcribes the genomic DNA (gDNA) into RNA, cloned genomic DNA results in a protein product thereby removing introns and splicing the RNA to form messenger RNA (mRNA), which is then translated into an MHC protein. Transfection of MHC molecules encoded by gDNA therefore facilitates reisolation of the gDNA, mRNA/cDNA, and protein. Production of MHC molecules in non-mammalian cell lines such as insect and bacterial cells requires cDNA clones, as these lower cell types do not have the ability to splice introns out of RNA transcribed from a gDNA clone. In these instances the mammalian gDNA transfectants of the present invention provide a valuable source of RNA which can be reverse transcribed to form MHC cDNA. The cDNA can then be cloned, transferred into cells, and then translated into protein. In addition to producing secreted MHC, such gDNA transfectants therefore provide a ready source of mRNA, and therefore cDNA clones, which can then be transfected into non-mammalian cells for production of MHC. Thus, the present invention which starts with MHC genomic DNA clones allows for the production of MHC in cells from various species.

A key advantage of starting from gDNA is that viable cells containing the MHC molecule of interest are not needed. Since all individuals in the population have a different MHC repertoire, one would need to search more than 500,000 individuals to find someone with the same MHC complement as a desired individual – this is observed when trying to find a match for bone marrow transplantation. Thus, if it is desired to produce a particular MHC molecule for use in an experiment or diagnostic, a person or cell expressing the MHC allele of interest would first need to be identified. Alternatively, in the method of the present invention, only a saliva sample, a hair root, an old freezer sample, or less than a milliliter (0.2 ml) of blood would be required to isolate the gDNA. Then, starting from gDNA, the MHC molecule of interest could be obtained via a gDNA clone as described

herein, and following transfection of such clone into mammalian cells, the desired protein could be produced directly or in mammalian cells or from cDNA in several species of cells using the methods of the present invention described herein.

Current experiments to obtain an MHC allele for protein expression typically start from mRNA, which requires a fresh sample of mammalian cells that *express* the MHC molecule of interest. Working from gDNA does not require gene expression or a fresh biological sample. It is also important to note that RNA is inherently unstable and is not easily obtained as is gDNA. Therefore, if production of a particular MHC molecule starting from a cDNA clone is desired, a person or cell line that is expressing the allele of interest must traditionally first be identified in order to obtain RNA. Then a fresh sample of blood or cells must be obtained; experiments using the methodology of the present invention show that $\geq$5 milliliters of blood that is less than 3 days old is required to obtain sufficient RNA for MHC cDNA synthesis. Thus, by starting with gDNA, the breath of MHC molecules that can be readily produced is expanded. This is a key factor in a system as polymorphic as the MHC system; hundreds of MHC molecules exist, and not all MHC molecules are readily available. This is especially true of MHC molecules unique to isolated populations or of MHC molecules unique to ethnic minorities. Starting class I or class II protein expression from the point of genomic DNA simplifies the isolation of the gene of interest and insures a more equitable means of producing MHC molecules for study; otherwise, one would be left to determine whose MHC molecules are chosen and not chosen for study, as well as to determine which ethnic population from which fresh samples cannot be obtained should not have their MHC molecules included in a diagnostic assay.

While cDNA may be substituted for genomic DNA as the starting material, production of cDNA for each of the desired HLA class I types will require hundreds of different, HLA typed, **viable** cell lines, each expressing a different HLA class I type. Alternatively, fresh samples are required from individuals with the various desired MHC types. The use of genomic DNA as the starting material allows for the production of clones for many HLA

molecules from a single genomic DNA sequence, as the amplification process can be manipulated to mimic recombinatorial and gene conversion events. Several mutagenesis strategies exist whereby a given class I gDNA clone could by modified at either the level of gDNA or at the cDNA resulting from this gDNA clone. The process of the present invention does not require viable cells, and therefore the degradation which plagues RNA is not a problem. Thus, from a given gDNA clone, any number of gDNA and cDNA MHC molecules can be produced. Three useful products can be obtained from the mammalian cell line expressing HLA class I molecules from such a genomic DNA construct. The first product is the soluble class I MHC protein, which may be purified and utilized in various experimental strategies, including but not limited to epitope testing. Epitope testing is a method for determining how well discovered or putative peptide epitopes bind individual, specific class I or class II MHC proteins. Epitope testing with secreted individual MHC molecules has several advantages over the prior art, which utilized MHC from cells expressing multiple membrane-bound MHCs. While the prior art method could distinguish if a cell or cell lysate would recognize an epitope, such method was unable to directly distinguish in which specific MHC molecule the peptide epitope was bound. Lengthy purification processes might be used to try and obtain a single MHC molecule, but doing so limits the quantity and usefulness of the protein obtained. The novelty of the current approach is that individual MHC specificities can be utilized in sufficient quantity through the use of recombinant, soluble MHC proteins. Because MHC molecules participate in numerous immune responses, studies of vaccines, transplantation, immune tolerance, and autoimmunity can all benefit from individual MHC molecules provided in sufficient quantity. A second important product obtained from mammalian cells secreting individual MHC molecules is the peptide cargo carried by MHC molecules. Class I and class II MHC molecules are really a trimolecular complex consisting of an alpha chain, a beta chain, and the alpha/beta chain's peptide cargo

to be reviewed by immune effector cells. Since it is the peptide cargo, and not the MHC alpha and beta chains, which marks a cell as infected, tumorigenic, or diseased, there is a great need to characterize the peptides bound by particular MHC molecules. For example, characterization of such peptides will greatly aid in determining how the peptides presented by a person with MHC-associated diabetes differ from the peptides presented by the MHC molecules associated with resistance to diabetes. As stated above, having a sufficient supply of an individual MHC molecule, and therefore that MHC molecules bound peptides, provides a means for studying such diseases. Because the method of the present invention provides quantities of MHC protein previously unobtainable, unparalleled studies of MHC molecules and their important peptide cargo can now be facilitated.

Another use for the peptides eluted from the secreted class I and class II molecules is the formation of predictive databases. Predictive databases and algorithms are used to select epitopes for inclusion in a vaccine or immunosuppressive therapy. However, the usefulness of such predictive algorithms is completely dependent upon the information which is used to build the algorithm or database. The substantial amount of peptide available from secreted class I and class II MHC molecules will result in more accurate algorithms and databases. For example, the amount of peptides obtained from secreted class I molecules in a bioreactor produces extended peptide motifs; more information can be gathered about the peptide population which is bound by a particular MHC molecule. In addition, more peptide allows for the systematic characterization of individual peptide ligands. In the past only the most prevalent individual peptides could be sequenced because there was only enough peptide available for these "dominant" peptide ligands. However, with our secreted MHC products we can amino acid sequence numerous dominant and subdominant peptide ligands. Subdominant peptide ligands are postulated to be important vaccine epitopes. Thus, providing more secretion and bioreactor production of

MHC results in a substantially better understanding of peptide ligands. A better understanding of the peptide ligands which bind MHC proteins in turn leads to more accurate algorithms and ligand databases which are essential for identifying and selecting vaccine epitopes for presentation to the immune system by MHC molecules.

A third useful product which can be obtained from the mammalian cell line expressing such a genomic DNA construct is a cDNA clone encoding the desired class I or class II molecule. The cDNA clone encoding the desired class I or class II molecule is formed from the mRNA molecule encoding the desired class I molecule isolated from such mammalian cell line. The cDNA clone may be utilized for functional testing, as described in more detail herein below. Thus, gDNA clones can be used as a mechanism to obtain cDNA clones of the desired class I or class II HLA molecule.

The cDNA clones may be transfected into a cell which is unable to splice introns and process the mRNA molecule and therefore would not express the MHC molecule encoded by the genomic DNA, such as insect cells or bacterial cells. In addition, these cell lines will also be deficient in peptide processing and loading, and therefore the soluble MHC molecules expressed from such cells will not contain peptides bound therein (referred to as free heavy chain HLA). Such soluble, free heavy chain HLA can effectively be tested for epitope binding as well. That is, MHC made in cells which do not naturally load peptide can be experimentally loaded with the peptide of choice. The heavy chain, light chain, peptide trimer can be reassembled in vitro using a high affinity peptide to facilitate assembly. Alternatively, a cell deficient in peptide processing can be pulsed with peptide such that the trimolecular MHC complex forms. DNA encoding a peptide (also encoding an appropriate targeting signal) could also be co-transfected into the cell with the MHC so that the MHC molecule which emerges from the cell is loaded only with the desired peptide. In this way MHC molecules could be loaded with a single low affinity peptide so that replacement with test peptides in a binding assay are more controlled.

Note that an advantage of secreting individual MHC molecules from a cell that naturally loads peptide is that the MHC molecule of interest is naturally loaded with

thousands of different peptides. When used in a peptide binding assay, a synthetic peptide can therefore be compared to thousands of naturally loaded peptides.

For functional testing, the peptide-MHC complex can be multimerized to form soluble peptide-MHC dimers or tetramers, which serve as ligands for CTLs. The tetramers can be mixed with CTLs *in vitro* or with CTLs from the blood of human subjects to identify antigenic peptides responsible for immune responses in humans. Altman et al (Science, 1996), herein expressly incorporated by reference, disclose a method of functional testing using tetramer technology; however, the method of Altman only discloses one soluble MHC molecule which has been utilized in such a method, and Altman's method faces the same disadvantages and defects described above for the prior art, that is, the method envisions isolating individual mRNA/cDNA molecules from hundreds of different, typed cell lines, and then manipulating the cDNA molecules to produce the desired soluble MHC molecule. The methods of the present invention envision combining the tetramer technology with amplification of genomic DNA, cloning the genomic DNA fragment and transfection of the resulting construct into a mammalian cell line followed by isolation of cDNA from such transfected cell line and transfection into a cell line deficient in peptide processing and loading, thereby removing the need to isolate hundreds of different, typed cell lines for obtaining the different cDNAs.

Alternatively, a cell line deficient in peptide processing but still efficient in peptide loading may be utilized for both epitope and functional testing, so that a putative epitope can be expressed or pulsed into a cell and loaded into the HLA molecule in the ER of such cell. The cDNA construct isolated as described above may be ligated into a mammalian expression vector which also contains a DNA fragment encoding a peptide of interest attached to a fragment encoding a signal peptide so that the peptide of interest will be retained in the ER of the cell for loading, and such construct transfected into the mammalian cell line deficient in peptide processing but which retains the ability to load peptide in the HLA molecules, such as the T2 cell line. In this manner, the peptide of interest is produced together with the HLA molecule. The soluble HLA molecule (with or

without a His or biotinylation signal tail) can then be purified and utilized as a reagent that has been produced in mammalian cells (fully glycosylated, etc.) and is loaded with the single co-transfected peptide. Optionally, random oligomers could be made and cloned into such a mammalian expression vector, and the soluble HLA molecules could again be purified and used to characterize T cells or other immune effector cells. In a further alternative, rather than expressing the peptides with the HLA molecule, the cells expressing the HLA molecule could be pulsed with a single synthetic peptide or multiple synthetic peptides and analyzed as described above to identify bound peptides. Any of the HLA molecule-peptide complexes could be multimerized to form dimers, tetramers, etc. and tested for their ability to serve as ligands for CTLs and induce immune responses in humans.

In summary, the method of the present invention involves production of MHC class I and class II molecules beginning from gDNA. The gDNA clones encoding a given MHC molecule can be truncated to be secreted rather than bound at the cell surface. This truncated version of the MHC molecule can be produced in mammalian or insect/bacterial cells such that milligram or greater quantities of an individual class I or class II molecule can be obtained. The secreted MHC class I molecules can be naturally loaded with thousands of endogenous peptides in mammalian cells, while the secreted MHC class II molecules can be naturally loaded with thousands of endocytic peptides in mammalian cells. Alternatively, the secreted MHC proteins can be produced in cells that do not load the MHC molecule with peptide ligand. Production of MHC proteins in cells which do not load the MHC molecule with peptide facilitates the loading of the MHC molecule via co-transfection with constructs encoding a given peptide(s). Alternatively, the MHC peptide-loading deficient MHC transfectant can be pulsed with peptides or DNA encoding peptides. The resulting individual secreted MHC molecules are useful for studies of peptide loading (i.e. in vaccine development), for characterizing human immune responses to a given MHC molecule loaded with a particular peptide(s), and to the development of diagnostics where one needs sufficient MHC protein in order to directly assess reactivity to different MHC proteins.

Another important component of the secreted MHC molecules described here is that naturally loaded peptides can be eluted from the MHC molecules and characterized. Substantial quantities of peptide can be obtained from individual MHC molecules, and the peptides can be selectively characterized. Unique information results from having a sufficient supply of eluted peptide, and this information is essential to databases and predictive algorithms which are essential to the vaccine architect.

Attached hereto are copies of several laboratory notebooks and the dissertation of Kiley R. Prilliman which provide exemplary drawings, experimentation, results and laboratory procedures in accordance with the present invention. Such information is to be understood to be included within the Specification. However, it is to be understood that the information contained therein is provided for the purpose of description, and the present invention is not limited to such exemplary information contained therein. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Thus, in accordance with the present invention, there has been provided a methodology for producing and manipulating Class I and Class II MHC molecules from gDNA that fully satisfies the objectives and advantages set forth herein above. Although the invention has been described in conjunction with the specific drawings, experimentation, results and language set forth herein above, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the invention.

OTD DISCLOSURE NO: 01HSC028 **DATE RECEIVED OTD:** 3/09/01

UNIVERSITY OF OKLAHOMA
PROPRIETARY INFORMATION/INVENTION DISCLOSURE

NOTE: This statement shall be treated as confidential information except for specific sections as noted. Except for individuals engaged in the evaluation and approval process, the information will not be divulged to others without proper confidentiality agreements in place, except as required by law. The objective of the form is to obtain the information necessary to determine whether to pursue patent protection for your invention.

SECTION I
NONCONFIDENTIAL INFORMATION

1. **Nonconfidential title of the work:**

   HLA Protein Production From cDNA

2. **Nonconfidential lay abstract of invention:**

   The present invention envisions a method of producing major histocompatibility complex (MHC) molecules, designated HLA class I and HLA class II in humans. The genes for these MHC molecules have been engineered from cDNA so that they are secreted from mammalian cells in a bioreactor unit.

3. **Nature of work:** **Machine** ☐ **Process** ☒ **Utility** ☐ **Software** ☐

   If Software: Have proper copyright markings been utilized? **Yes** ☐ **No** ☐

OFFICE OF TECHNOLOGY DEVELOPMENT

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Telephone (405) 271-2090
Fax (405) 271-8651

4. Please list all submitters below:

Submitters	Office Mailing Address	% of Contribution*	Office Phone No.	Citizenship
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b. Heather D. Hickman	OUHSC 975 NE 10th Street, BRC 317 Oklahoma City, OK 73104	10	(405)271-1203	US
c. Kiley R. Prilliman	8284 Flanders Drive #57 San Diego, CA 92126	10	(858)678-4552	US
d. Sean Turner	800 N Research Pkwy, Suite 414 Oklahoma City, OK 73104	10	(405)271-3838	United Kingdom
e.			( )	

*NOTE: This % of contribution is an estimate providing for the division of proceeds, and not an assessment of legal inventorship. If this column is blank, submitters will share equally any revenues generated based on information contained in this disclosure.

5. If you have any other affiliations (i.e. received salary from another party, housed in other facilities besides university facilities), please list below:

Submitters	Other Affiliations	% of Salary Other Affiliation Paid
a. William H. Hildebrand	Pure Protein, L.L.C. Consultant	0
b. Heather D. Hickman	none	0
c. Kiley R. Prilliman	LaHoya Institute of Allergy and Immunology	100
d. Sean Turner	Pure Protein, L.L.C. Consultant	100
e.		

6. Has a Conflict of Interest form been filed with the Provost's office? Yes ☒ No ☐

7. List specific University research support as well as external funding. List all sources, including matching funds.

   a. Name of sponsoring agency, company, or internal funding
   The soluble HLA Class I technology described here was licensed to Pure Protein, L.L.C. The Licensing Agreement was filed between OU and Pure Protein, L.L.C. 6/3/99. Work for the soluble HLA Class II technology was supported through Sponsored Research Agreements (ORA#20000017 and ORA#20010109) between OU and Pure Protein, L.L.C

   b. Principal Investigator
   William H. Hildebrand

   c. Co-Investigators; Consultants

d. Grant or Project Number
OU-Pure Protein, L.L.C. Licensing Agreement filed 6/3/99
OU-Pure Protein, L.L.C. Sponsored Research Agreements ORA#20000017 and ORA#20010109

e. University Account Code
C7000901 and C7000902

f. Attach copy of Grant or Contract Document.

Has a biological, chemical or physical material or substance obtained from others been used in the creation of this invention? Yes ☒ No ☐

If Yes, was a Materials Transfer Agreement or similar document used to obtain the material or substance? Yes ☒ No ☐ See DoD Grant#N00014-95-1-0074

If Yes, attach a copy of the agreement.

If No, identify source and explain.

GENERAL PATENT INFORMATION

In order to obtain patent protection, your invention must demonstrate the following:

1. New (or novel): The invention must be new, that is, it has not been previously used, sold or described publicly.

2. Useful: The invention must have an actual use and not be just a subject for additional research.

3. Non-obvious: The invention must not be obvious at the time of conception to another person having ordinary skill in the art.

The patent laws set forth those classes of inventions eligible for patenting as follows:

1. Machines

2. Processes

3. Compositions of Matter

4. Manufacture

SECTION II
PROPRIETARY INFORMATION
DOCUMENTATION

OBJECTIVE: To define the nature, purpose and operation of the invention, a practical presentation is preferable to highly theoretical material.

EVENTS	DATE	SUPPORTING DOCUMENTATION
1. Initial Idea	10/22/93	See Mary Ellexson's Laboratory notebook #1 pp7-53
2. First oral or written description of information. (Please provide copy of witnessed lab notebook showing date of discovery.)	3/1/94	NIH contract#NO1-AI-45243 , See Mary Ellexson's Laboratory notebook #1 pp7-53. See Kiley Prilliman's laboratory notebook #2 pp076 through notebook #14 pp68. See Sean Turner's sHLA Class II notebook #1 and #2.
3. Level of testing completed (Lab scale, prototype, etc.)	10/22/93	See Mary Ellexson's Laboratory notebook #1 pp7-53. See Kiley Prilliman's laboratory notebook #2 pp076 through notebook #14 pp68. See Sean Turner's sHLA Class II notebook #1 and #2.
4. Prototype completed	10/22/93	See Mary Ellexson's Laboratory notebook #1 pp7-53. See Kiley Prilliman's laboratory notebook #2 pp076 through notebook #14 pp68. See Sean Turner's sHLA Class II notebook #1 and #2.
5. First written or oral publication date (include date of printed abstracts, any oral presentations, or electronic publication dates of journals, poster presentations, presentations to industry etc.) Attach copies.	10/3/96	Prilliman, K et al Large-scale production of class I bound peptides: assigning a signature to HLA-B*1501. Immunogenetics 45: 379-385, 1997.
6. Other external oral or written disclosures.	12/17/99 12/18/00	Patent Applications filed by Joe Long 12/17/99, Docket#6680.002, Patent Application 09/461,321 and Dunlap, Codding, and Rogers, P.C. 12/18/00, Docket#6680.003, Patent Application 60/256,410.

7. **Provide a full description of the proprietary information. This information should be in such detail as to "teach" the invention and to provide the basis for a patent application. Someone skilled in the art should be able to reproduce the invention within a reasonable period of time based on the information supplied here.**

   a. **Complete detailed description of invention (attach separate sheets if necessary):**

      See Attached Summary/HLA Protein Production From Genomic DNA and Patent Application entitled Equipment and Process for Production of pure major histocompatibility complex (MHC) antigens in human cells for borad Immunology testing and Therapeutic Use

   b. **Provide a complete description of the State of the Art prior to your invention. Include a list of any literature references, patent applications, or issued patents you are aware of. Cite source of literature or patent search information. (Attach separate sheets if necessary.)**

      See Attached Summary

   c. **Describe the advantages, improvements and technical impact of your invention over existing practice (novel or unusual features):**

      See Attached Summary

d. List the areas of applications of invention indicating the problem solved in the area by your invention:

See Attached Summary

e. List the main advantages of the invention (list in the order as the advantages would relate to the list of applications in item d. above):

See Attached Summary

f. List any known disadvantages using the same format as above:

See Attached Summary

8. Describe the state of development of your invention? Is there a prototype or samples of materials available for viewing or testing? Include any test results available.

See Mary Ellexson's Laboratory notebook #1 pp7-53. See Kiley Prilliman's laboratory notebook #2 pp076 through notebook #14 pp68. See Sean Turner's sHLA Class II notebook #1 and #2.

9. Outline the further research and development, if any, that would greatly enhance the state of development of the invention.

See Attached Summary

10. List any funded or submitted proposals that have been submitted previously based on this invention. Were proprietary markings affixed to the proposal?

11. Attach any pertinent tables or drawings describing the invention.

12. Provide any other comments you may have regarding your proprietary information.

13. Provide the date and description of all planned publications, oral presentations, poster sessions, abstracts, preprints, or other public dissemination of the invention. (Check to see if the journal publishes electronically and provide OTD with the earliest of the dates.)

DATE	DESCRIPTION
Unknown	Unknown

14. Submitter's signatures (this disclosure is submitted under the University of Oklahoma Intellectual Property Policy, Patents, Paragraph 1.1.)

In consideration of employment or a consulting relationship, and subject to any prior agreements with The University of Oklahoma Board of Regents, this invention/discovery is hereby assigned to The University of Oklahoma Board of Regents, together with all patents covering said invention/discovery.

Signature	Date	Home Address / City, State, Zip
Keith H Hakes	3-7-01	900 Northcreek Drive Edmond, OK 73034
Heather D Hickman	3/07/01	7901 N 120th Ave. Owasso, OK 74055
Kelly Pri Ullman	3/7/01	8284 Flanders Drive, #57 San Diego, CA 92126
Brent Turner	3/7/01	4095 McDonald Road Choctaw, OK 73020

15. Invention Disclosed to and Understood By (Witness):

Signature _____ Date _____

16. Office of Technology Development

Signature _____ Date _____

SECTION III
COMMERCIAL POTENTIAL

NOTE: The information contained in this section will not be distributed to anyone outside of the University of Oklahoma, except as required by law.

1. **Where would your idea have commercial value?**

U.S.	☒	South America	☐	Africa	☐
Canada	☐	Japan	☐	Australia	☐
Europe	☐	Asia	☐	Other	☒ PCT countries to be determined.

2. **In your judgment, does the proprietary information require copyright or patent protection in order to be successfully marketed:**

a. **Patent protection** ☒
b. **Copyright protection** ☒
c. **Know-How could be licensed** ☒

3. **List any companies, and individuals within those companies, that you feel may have a commercial interest in licensing the invention. (Indicate by special note those companies that have contacted you regarding the invention.)**

The soluble HLA Class I technology described here was licensed to Pure Protein, L.L.C. The Licensing Agreement was filed between OU and Pure Protein, L.L.C. 6/3/99. Work for the soluble HLA Class II technology was supported through Sponsored Research Agreements (ORA#20000017 and ORA#20010109) between OU and Pure Protein, L.L.C.

A Patent Application for this technology has been filed by the law offices of Joe Long 12/17/99, Docket#6680.002, Patent Application 09/461,321 and Dunlap, Codding, and Rogers, P.C. 12/18/00, Docket#6680.003, Patent Application 60/256,410.

HLA PROTEIN PRODUCTION FROM GENOMIC DNA

Before explaining at least one embodiment of the invention in detail by way of exemplary drawings, experimentation, results, and laboratory procedures, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings, experimentation and/or results. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Class I major histocompatibility complex (MHC) molecules, designated HLA class I in humans, bind and display peptide antigens upon the cell surface. The peptides they present are derived from either normal endogenous proteins ("self") or foreign proteins ("nonself"), such as products of malignant transformation or intracellular pathogens such as viruses. In this manner, class I molecules convey information regarding the internal fitness of a cell to immune effector cells including but not limited to $CD8^+$ cytotoxic T lymphocytes (CTLs), which are activated upon interaction with "nonself" peptides and which lyse or kill the cell presenting such "nonself" peptides.

Class II MHC molecules, designated HLA class II in humans, also bind and display peptide antigens upon the cell surface. However, unlike class I MHC molecules which are expressed on virtually all nucleated cells, class II MHC molecules are normally confined to specialized cells, such as B lymphocytes, macrophages, dendritic cells, and other antigen presenting cells which take up foreign antigens from the extracellular fluid via an endocytic pathway. Therefore, the peptides they bind and present are derived from extracellular foreign antigens, such as products of bacteria that

multiply outside of cells, wherein such products include protein toxins secreted by the bacteria that have deleterious and even lethal effects on the host. In this manner, class II molecules convey information regarding the fitness of the extracellular space in the vicinity of the cell displaying the class II molecule to immune effector cells including but not limited to $CD4^+$ helper T cells, which help eliminate such pathogens both by helping B cells make antibodies against microbes as well as toxins produced by such microbes and by activating macrophages to destroy ingested microbes.

Class I and class II HLA molecules exhibit extensive polymorphism, which is generated by systematic recombinatorial and point mutation events; as such, hundreds of different HLA types exist throughout the world's population, resulting in a large immunological diversity among the population. Such extensive HLA diversity in the population results in tissue or organ transplant rejection between individuals as well as differing susceptibilities and/or resistances to infectious diseases. HLA molecules also contribute significantly to autoimmunity and cancer. Because HLA molecules mediate most, if not all, adaptive immune responses, HLA proteins are needed to study transplantation, autoimmunity, and for developing vaccines.

There are several applications in which purified, individual class I and class II MHC proteins would be highly useful. Such applications include using MHC-peptide multimers as immunodiagnostic reagents for disease resistance/autoimmunity; assessing the binding of potentially therapeutic peptides; elution of peptides from MHC molecules to identify vaccine candidates; screening transplant patients for preformed MHC specific antibodies; and removal of anti-HLA antibodies from a patient. Since every individual has different MHC molecules, the testing of numerous individual MHC molecules is a prerequisite for understanding differences in disease susceptibility between individuals. Therefore, purified MHC molecules

representative of the hundreds of different HLA types existing throughout the world's population are highly desirable for unraveling disease susceptibilities and resistances and for designing therapeutics.

Currently there is no readily available source of individual HLA molecules. Until now, the quantities of HLA protein available are small and typically consist of a mixture of different HLA molecules. Production of HLA molecules traditionally involves growth and lysis of cells expressing multiple HLA molecules. Ninety percent of the population is heterozygous at each of the HLA loci; codominant expression results in multiple HLA proteins expressed at each HLA locus. To purify native class I or class II molecules from mammalian cells requires time-consuming and cumbersome purification methods, and since each cell typically expresses multiple surface-bound HLA class I or class II molecules, HLA purification results in a mixture of many different HLA class I or class II molecules. When performing experiments using such a mixture of HLA molecules or performing experiments using a cell having multiple surface-bound HLA molecules, interpretation of results cannot *directly* distinguish between the different HLA molecules, and one cannot be certain that any particular HLA molecule is responsible for a given result. Therefore, a need exists in the art for a method of producing substantial quantities of individual HLA class I or class II molecules so that they can be readily purified and isolated independent of other HLA class I or class II molecules. Such individual HLA molecules, when provided in sufficient quantity and purity, would provide a powerful tool for studying and measuring immune responses.

The present invention envisions a method of producing MHC molecules which are secreted from mammalian cells in a bioreactor unit. Substantial quantities of individual MHC molecules are obtained by modifying class I or class II molecules so they are secreted. Secretion of soluble MHC molecules

overcomes the disadvantages and defects of the prior art in relation to the quantity and purity of MHC molecules produced. Problems of quantity are overcome because the cells producing the MHC do not need to be detergent lysed or killed in order to obtain the MHC molecule. In this way the cells producing secreted MHC remain alive and therefore continue to produce MHC. Problems of purity are overcome because the only MHC molecule secreted from the cell is the one that has specifically been constructed to be secreted. Thus, transfection of vectors encoding such secreted MHC molecules into cells which may express endogenous, surface bound MHC provides a method of obtaining a highly concentrated form of the transfected MHC molecule as it is secreted from the cells. Greater purity can be assured by transfecting the secreted MHC molecule into MHC deficient cell lines.

Production of the MHC molecules in a hollow fiber bioreactor unit allows cells to be cultured at a density substantially greater than conventional liquid phase tissue culture permits. Dense culturing of cells secreting MHC molecules further amplifies the ability to continuously harvest the transfected MHC molecules. Dense bioreactor cultures of MHC secreting cell lines allow for high concentrations of individual MHC proteins to be obtained. Highly concentrated individual MHC proteins provide an advantage in that most downstream protein purification strategies perform better as the concentration of the protein to be purified increases. Thus, the culturing of MHC secreting cells in bioreactors allows for a continuous production of individual MHC proteins in a concentrated form.

The method of the present invention begins by obtaining genomic or complementary DNA which encodes the desired MHC class I or class II molecule. Alleles at the locus which encode the desired MHC molecule are PCR amplified in a locus specific manner. These locus specific PCR products may include the entire coding region of the MHC molecule or a portion

thereof. In some cases a nested or hemi-nested PCR is applied to produce a truncated form of the class I or class II gene so that it will be secreted rather than anchored to the cell surface. In other cases the PCR will directly truncate the MHC molecule.

Locus specific PCR products are cloned into a mammalian expression vector and screened with a variety of methods to identify a clone encoding the desired MHC molecule. The cloned MHC molecules are DNA sequenced to insure fidelity of the PCR. Faithful truncated clones of the desired MHC molecule are then transfected into a mammalian cell line. When such cell line is transfected with a vector encoding a recombinant class I molecule, such cell line may either lack endogenous class I expression or express endogenous class I. It is important to note that cells expressing endogenous class I may spontaneously release MHC into solution upon natural cell death. In cases where this small amount of spontaneously released MHC is a concern, the transfected class I MHC molecule can be "tagged" such that it can be specifically purified away from spontaneously released endogenous class I molecules in cells that express class I molecules. For example, a DNA fragment encoding a His tail which will be attached to the protein may be added by the PCR reaction or may be encoded by the vector into which the gDNA fragment is cloned, and such His tail will further aid in purification of the class I molecules away from endogenous class I molecules. Tags beside a histidine tail have also been demonstrated to work and are logical to those skilled in the art of tagging proteins for downstream purification.

Cloned genomic DNA fragments contain both exons and introns as well as other non-translated regions at the 5' and 3' termini of the gene. Following transfection into a cell line which transcribes the genomic DNA (gDNA) into RNA, cloned genomic DNA results in a protein product thereby removing introns and splicing the RNA to form messenger RNA (mRNA),

which is then translated into an MHC protein. Transfection of MHC molecules encoded by gDNA therefore facilitates reisolation of the gDNA, mRNA/cDNA, and protein. Production of MHC molecules in non-mammalian cell lines such as insect and bacterial cells requires cDNA clones, as these lower cell types do not have the ability to splice introns out of RNA transcribed from a gDNA clone. In these instances the mammalian gDNA transfectants of the present invention provide a valuable source of RNA which can be reverse transcribed to form MHC cDNA. The cDNA can then be cloned, transferred into cells, and then translated into protein. In addition to producing secreted MHC, such gDNA transfectants therefore provide a ready source of mRNA, and therefore cDNA clones, which can then be transfected into non-mammalian cells for production of MHC. Thus, the present invention which starts with MHC genomic DNA clones allows for the production of MHC in cells from various species.

A key advantage of starting from gDNA is that viable cells containing the MHC molecule of interest are not needed. Since all individuals in the population have a different MHC repertoire, one would need to search more than 500,000 individuals to find someone with the same MHC complement as a desired individual – this is observed when trying to find a match for bone marrow transplantation. Thus, if it is desired to produce a particular MHC molecule for use in an experiment or diagnostic, a person or cell expressing the MHC allele of interest would first need to be identified. Alternatively, in the method of the present invention, only a saliva sample, a hair root, an old freezer sample, or less than a milliliter (0.2 ml) of blood would be required to isolate the gDNA. Then, starting from gDNA, the MHC molecule of interest could be obtained via a gDNA clone as described herein, and following transfection of such clone into mammalian cells, the desired protein could be produced directly or in mammalian cells or from cDNA in

several species of cells using the methods of the present invention described herein.

Current experiments to obtain an MHC allele for protein expression typically start from mRNA, which requires a fresh sample of mammalian cells that *express* the MHC molecule of interest. Working from gDNA does not require gene expression or a fresh biological sample. It is also important to note that RNA is inherently unstable and is not easily obtained as is gDNA. Therefore, if production of a particular MHC molecule starting from a cDNA clone is desired, a person or cell line that is expressing the allele of interest must traditionally first be identified in order to obtain RNA. Then a fresh sample of blood or cells must be obtained; experiments using the methodology of the present invention show that $\geq$5 milliliters of blood that is less than 3 days old is required to obtain sufficient RNA for MHC cDNA synthesis. Thus, by starting with gDNA, the breath of MHC molecules that can be readily produced is expanded. This is a key factor in a system as polymorphic as the MHC system; hundreds of MHC molecules exist, and not all MHC molecules are readily available. This is especially true of MHC molecules unique to isolated populations or of MHC molecules unique to ethnic minorities. Starting class I or class II protein expression from the point of genomic DNA simplifies the isolation of the gene of interest and insures a more equitable means of producing MHC molecules for study; otherwise, one would be left to determine whose MHC molecules are chosen and not chosen for study, as well as to determine which ethnic population from which fresh samples cannot be obtained should not have their MHC molecules included in a diagnostic assay.

While cDNA may be substituted for genomic DNA as the starting material, production of cDNA for each of the desired HLA class I types will require hundreds of different, HLA typed, **viable** cell lines, each expressing a

different HLA class I type. Alternatively, fresh samples are required from individuals with the various desired MHC types. The use of genomic DNA as the starting material allows for the production of clones for many HLA molecules from a single genomic DNA sequence, as the amplification process can be manipulated to mimic recombinatorial and gene conversion events. Several mutagenesis strategies exist whereby a given class I gDNA clone could by modified at either the level of gDNA or at the cDNA resulting from this gDNA clone. The process of the present invention does not require viable cells, and therefore the degradation which plagues RNA is not a problem. Thus, from a given gDNA clone, any number of gDNA and cDNA MHC molecules can be produced. Three useful products can be obtained from the mammalian cell line expressing HLA class I molecules from such a genomic DNA construct. The first product is the soluble class I MHC protein, which may be purified and utilized in various experimental strategies, including but not limited to epitope testing. Epitope testing is a method for determining how well discovered or putative peptide epitopes bind individual, specific class I or class II MHC proteins. Epitope testing with secreted individual MHC molecules has several advantages over the prior art, which utilized MHC from cells expressing multiple membrane-bound MHCs. While the prior art method could distinguish if a cell or cell lysate would recognize an epitope, such method was unable to directly distinguish in which specific MHC molecule the peptide epitope was bound. Lengthy purification processes might be used to try and obtain a single MHC molecule, but doing so limits the quantity and usefulness of the protein obtained. The novelty of the current approach is that individual MHC

specificities can be utilized in sufficient quantity through the use of recombinant, soluble MHC proteins. Because MHC molecules participate in numerous immune responses, studies of vaccines, transplantation, immune tolerance, and autoimmunity can all benefit from individual MHC molecules provided in sufficient quantity. A second important product obtained from mammalian cells secreting individual MHC molecules is the peptide cargo carried by MHC molecules. Class I and class II MHC molecules are really a trimolecular complex consisting of an alpha chain, a beta chain, and the alpha/beta chain's peptide cargo to be reviewed by immune effector cells. Since it is the peptide cargo, and not the MHC alpha and beta chains, which marks a cell as infected, tumorigenic, or diseased, there is a great need to characterize the peptides bound by particular MHC molecules. For example, characterization of such peptides will greatly aid in determining how the peptides presented by a person with MHC-associated diabetes differ from the peptides presented by the MHC molecules associated with resistance to diabetes. As stated above, having a sufficient supply of an individual MHC molecule, and therefore that MHC molecules bound peptides, provides a means for studying such diseases. Because the method of the present invention provides quantities of MHC protein previously unobtainable, unparalleled studies of MHC molecules and their important peptide cargo can now be facilitated.

Another use for the peptides eluted from the secreted class I and class II molecules is the formation of predictive databases. Predictive databases and algorithms are used to select epitopes for inclusion in a vaccine or immunosuppressive therapy. However, the usefulness of such predictive

algorithms is completely dependent upon the information which is used to build the algorithm or database. The substantial amount of peptide available from secreted class I and class II MHC molecules will result in more accurate algorithms and databases. For example, the amount of peptides obtained from secreted class I molecules in a bioreactor produces extended peptide motifs; more information can be gathered about the peptide population which is bound by a particular MHC molecule. In addition, more peptide allows for the systematic characterization of individual peptide ligands. In the past only the most prevalent individual peptides could be sequenced because there was only enough peptide available for these "dominant" peptide ligands. However, with our secreted MHC products we can amino acid sequence numerous dominant and subdominant peptide ligands. Subdominant peptide ligands are postulated to be important vaccine epitopes. Thus, providing more secretion and bioreactor production of MHC results in a substantially better understanding of peptide ligands. A better understanding of the peptide ligands which bind MHC proteins in turn leads to more accurate algorithms and ligand databases which are essential for identifying and selecting vaccine epitopes for presentation to the immune system by MHC molecules.

A third useful product which can be obtained from the mammalian cell line expressing such a genomic DNA construct is a cDNA clone encoding the desired class I or class II molecule. The cDNA clone encoding the desired class I or class II molecule is formed from the mRNA molecule encoding the desired class I molecule isolated from such mammalian cell line. The cDNA clone may be utilized for functional testing, as described in more detail herein below. Thus, gDNA clones can be used as a mechanism to obtain

cDNA clones of the desired class I or class II HLA molecule.

The cDNA clones may be transfected into a cell which is unable to splice introns and process the mRNA molecule and therefore would not express the MHC molecule encoded by the genomic DNA, such as insect cells or bacterial cells. In addition, these cell lines will also be deficient in peptide processing and loading, and therefore the soluble MHC molecules expressed from such cells will not contain peptides bound therein (referred to as free heavy chain HLA). Such soluble, free heavy chain HLA can effectively be tested for epitope binding as well. That is, MHC made in cells which do not naturally load peptide can be experimentally loaded with the peptide of choice. The heavy chain, light chain, peptide trimer can be reassembled in vitro using a high affinity peptide to facilitate assembly. Alternatively, a cell deficient in peptide processing can be pulsed with peptide such that the trimolecular MHC complex forms. DNA encoding a peptide (also encoding an appropriate targeting signal) could also be co-transfected into the cell with the MHC so that the MHC molecule which emerges from the cell is loaded only with the desired peptide. In this way MHC molecules could be loaded with a single low affinity peptide so that replacement with test peptides in a binding assay are more controlled.

Note that an advantage of secreting individual MHC molecules from a cell that naturally loads peptide is that the MHC molecule of interest is naturally loaded with thousands of different peptides. When used in a peptide binding assay, a synthetic peptide can therefore be compared to thousands of naturally loaded peptides.

For functional testing, the peptide-MHC complex can be multimerized to form soluble peptide-MHC dimers or tetramers, which serve as ligands for CTLs. The tetramers can be mixed with CTLs *in vitro* or with CTLs from the blood of human subjects to identify antigenic peptides responsible for

immune responses in humans. Altman et al (Science, 1996), herein expressly incorporated by reference, disclose a method of functional testing using tetramer technology; however, the method of Altman only discloses one soluble MHC molecule which has been utilized in such a method, and Altman's method faces the same disadvantages and defects described above for the prior art, that is, the method envisions isolating individual mRNA/cDNA molecules from hundreds of different, typed cell lines, and then manipulating the cDNA molecules to produce the desired soluble MHC molecule. The methods of the present invention envision combining the tetramer technology with amplification of genomic DNA, cloning the genomic DNA fragment and transfection of the resulting construct into a mammalian cell line followed by isolation of cDNA from such transfected cell line and transfection into a cell line deficient in peptide processing and loading, thereby removing the need to isolate hundreds of different, typed cell lines for obtaining the different cDNAs.

Alternatively, a cell line deficient in peptide processing but still efficient in peptide loading may be utilized for both epitope and functional testing, so that a putative epitope can be expressed or pulsed into a cell and loaded into the HLA molecule in the ER of such cell. The cDNA construct isolated as described above may be ligated into a mammalian expression vector which also contains a DNA fragment encoding a peptide of interest attached to a fragment encoding a signal peptide so that the peptide of interest will be retained in the ER of the cell for loading, and such construct transfected into the mammalian cell line deficient in peptide processing but which retains the ability to load peptide in the HLA molecules, such as the T2 cell line. In this manner, the peptide of interest is produced together with the HLA molecule. The soluble HLA molecule (with or without a His or biotinylation signal tail) can then be purified and utilized as a reagent that has been produced in

mammalian cells (fully glycosylated, etc.) and is loaded with the single co-transfected peptide. Optionally, random oligomers could be made and cloned into such a mammalian expression vector, and the soluble HLA molecules could again be purified and used to characterize T cells or other immune effector cells. In a further alternative, rather than expressing the peptides with the HLA molecule, the cells expressing the HLA molecule could be pulsed with a single synthetic peptide or multiple synthetic peptides and analyzed as described above to identify bound peptides. Any of the HLA molecule-peptide complexes could be multimerized to form dimers, tetramers, etc. and tested for their ability to serve as ligands for CTLs and induce immune responses in humans.

In summary, the method of the present invention involves production of MHC class I and class II molecules beginning from gDNA. The gDNA clones encoding a given MHC molecule can be truncated to be secreted rather than bound at the cell surface. This truncated version of the MHC molecule can be produced in mammalian or insect/bacterial cells such that milligram or greater quantities of an individual class I or class II molecule can be obtained. The secreted MHC class I molecules can be naturally loaded with thousands of endogenous peptides in mammalian cells, while the secreted MHC class II molecules can be naturally loaded with thousands of endocytic peptides in mammalian cells. Alternatively, the secreted MHC proteins can be produced in cells that do not load the MHC molecule with peptide ligand. Production of MHC proteins in cells which do not load the MHC molecule with peptide facilitates the loading of the MHC molecule via co-transfection with constructs encoding a given peptide(s). Alternatively, the MHC peptide-loading deficient MHC transfectant can be pulsed with peptides or DNA encoding peptides. The resulting individual secreted MHC molecules are useful for studies of peptide loading (i.e. in vaccine

development), for characterizing human immune responses to a given MHC molecule loaded with a particular peptide(s), and to the development of diagnostics where one needs sufficient MHC protein in order to directly assess reactivity to different MHC proteins.

Another important component of the secreted MHC molecules described here is that naturally loaded peptides can be eluted from the MHC molecules and characterized. Substantial quantities of peptide can be obtained from individual MHC molecules, and the peptides can be selectively characterized. Unique information results from having a sufficient supply of eluted peptide, and this information is essential to databases and predictive algorithms which are essential to the vaccine architect.

Attached hereto are copies of several laboratory notebooks and the dissertation of Kiley R. Prilliman which provide exemplary drawings, experimentation, results and laboratory procedures in accordance with the present invention. Such information is to be understood to be included within the Specification. However, it is to be understood that the information contained therein is provided for the purpose of description, and the present invention is not limited to such exemplary information contained therein. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Thus, in accordance with the present invention, there has been provided a methodology for producing and manipulating Class I and Class II MHC molecules from gDNA that fully satisfies the objectives and advantages set forth herein above. Although the invention has been described in conjunction with the specific drawings, experimentation, results and language set forth herein above, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications

and variations that fall within the spirit and broad scope of the invention.

University of Oklahoma

THE BOARD OF REGENTS OF THE UNIVERSITY OF OKLAHOMA

INTELLECTUAL PROPERTY POLICY

PREAMBLE

The people of the State of Oklahoma may reasonably expect that their investments in the University of Oklahoma will create new industry and enhance existing industry within the State and Nation. Such new industry creates greater employment opportunities for citizens of the State and the Nation and an improvement in their standard of living.

The creation and development of intellectual property at the University encourages new business and is key to creating strong University and industry partnerships. It is the responsibility of University employees to disclose intellectual property and to foster an entrepreneurial attitude within the work force by involving students in the creation of intellectual property. Intellectual property development shall be pursued in concert with, but subject to, the University's principle responsibilities of education and knowledge creation.

Therefore, it is in the best interest of the University to adopt a policy that encourages disclosure of discoveries and inventions and rewards such creative activity. To do so, the University policy must insure inventors a share in any financial success enjoyed by the University through the creation and commercialization of intellectual property. The basic objectives of the University's policy concerning discoveries and inventions include the following:

a) To maintain the University's academic policy of encouraging research, publication, and scholarship independent of potential gain from royalties or other income.

b) To make patented materials created pursuant to University objectives available in the public interest under conditions that will promote their effective utilization and commercialization.

c) To provide adequate incentive and recognition to faculty and staff through proceeds derived from their works.

PATENTS

1. OWNERSHIP

1.1 All discoveries and inventions, whether patentable or unpatentable, and including any and all patents (domestic and foreign) based thereon and applications for such patents, which are made or conceived by any member of the faculty, staff, or student body of The University of Oklahoma, either in the course and/or scope of employment for The University of Oklahoma or substantially through the use of facilities or funds provided by or through the University shall be owned by and be the property of the Board of Regents of the University of Oklahoma except as described below.

1.2 The University Vice President for Technology Development may in collaboration with the appropriate originating campus Officers, negotiate ownership of discoveries/inventions with research sponsors when it is in the best interest of the University to do so. Otherwise, all rights are as described below.

1.3 Faculty having rights to discoveries/inventions prior to employment at the University of Oklahoma should notify the Office of Technology Development of such intellectual property so that ownership to any further development of that same intellectual property at the University of Oklahoma may be established, by written agreement, with the University Vice President for Technology Development. The Vice President for Technology Development shall consult with the Provost of the Health Sciences Center or his designee before entering a contract with faculty at the Heath Sciences Center.

1.4 In the event faculty or staff make discoveries or inventions outside the course of and/or scope of employment and using no University facilities, equipment, or supplies, or if using such reimburses the University for this use in accordance with a prior written agreement with the University and in accordance with University policy, title to such discoveries or inventions shall remain in the inventor, provided the University Vice President for Technology Development determines that the discovery or invention was made under these conditions. The inventor shall nonetheless submit a disclosure form to the Office of Technology Development. This disclosure shall contain sufficient information to enable the University Vice President for Technology Development to make a determination. If confidential information is required, the University will sign a nondisclosure agreement for purposes of this review. Should the University Vice President for Technology Development determine that the University does have a proprietary interest, a more complete disclosure may be required before making a decision in regard to title, the University Vice President for Technology Development shall consult with the Provost of the Health Sciences Center when the faculty member is based at the Health Sciences Center. If it is determined that the University has an interest, the provisions of this policy shall then be applicable. Appeals of such determinations may be made to the Faculty Appeals Board and then to the President.

1.5 All rights in and to discoveries and inventions described in Paragraph 1.1 shall be disclosed to and assigned to the Board of Regents of the University of Oklahoma as a specific condition of employment with the University and admission to and/or attendance at the University. Faculty, staff and students shall execute any and all documents the University deems reasonably necessary to evidence such ownership, meet its legal obligations and effect patent protection, domestic and foreign, for the University or its nominee. All costs involved in obtaining and maintaining patent protection shall be borne by the University or its nominee.

1.6 The University agrees to act in good faith with respect to the determination of ownership.

2. REVENUE

2.1 The gross revenues (which shall include but not be limited to, cash and equity) received by the University from the licensing, sale, or commercialization of a University discovery or invention as described in section 1, will be distributed among the discoverer(s)/inventor(s), his/her/their primary department(s) and the University, in accordance with the following formula:

35% of gross revenues to the discoverer(s)/inventor(s) (as submitted on the Invention Disclosure Form);

The remaining 65% to be used to reimburse the University for out-of-pocket expenses that it has or shall incur in connection with, but not limited to, patent filing, prosecution, maintenance, and defense;

After expenses have been recouped, the remaining 65% will be distributed as follows:

20% to originating college(s), half of which to go to the originating department
5% to President's discretionary fund
5% to the campus Vice President for Research
15% to OTD to apply to operational expenses with a pro rata share to go to the originating campus (at least 80%) Office of Technology Development
20% to the Growth Fund maintained for each originating campus

Stock certificates issued to the University shall be held by the Controllers Office of the Norman Campus.

The right to receive such royalty revenue shall be extended to the inventor(s) in the event that the inventor is no

longer an employee or student of the University. Such right shall also accrue to the estate of the inventor(s). Inventor(s) and/or their successors or assigns shall have the responsibility to provide the Office of Technology Development of the respective campuses with all the necessary information to make payments to the appropriate parties, including without limitation, current addresses; provided, failure to keep the University so informed shall permit the University to hold all such revenue for such parties for a reasonable time or until the lawful beneficiaries make claim thereto.

The University Vice President for Technology Development shall establish and maintain a "Growth Fund" for each originating campus to be used to stimulate general faculty intellectual property disclosures as well as technology development and transfer. The fund will be used to further stimulate researchers on each campus to make proposals when there is a need for additional funding to provide prototypes, additional research results, and/or "gap" funding to keep a program in place during transition. Those accessing the Fund will be expected to repay the fund at a target rate of two times the amount awarded from the fund. This fund will be administered under guidelines consistent with the research and scholarly missions of the University in consultation with the University Patent Committee. The Health Sciences Center Senior Vice President and Provost will confer with the University Vice President for Technology Development prior to the Provost's allocation of funds. If the University Vice President for Technology Development does not approve of the proposed allocation, the proposed allocation will be submitted to the President for final approval or disapproval.

2.2 When there are two or more discoverers/inventors, each shall share equally in the inventor's share unless all discoverers/inventors agree in writing to a different distribution of such share. Such originally-signed agreement shall be filed with the Office of Technology Development of the respective campuses of the discoverer(s)/inventor(s). No distribution of cash revenues will be made until this issue is resolved by the discoverer(s)/inventor(s) or their successors in interest.

2.3 The discoverer(s)/inventor(s) and his or her college shall be paid their share of the cash revenues upon receipt of the University and will be furnished with a statement of revenue derived from the commercialization of the invention at the time of payment. In the event of any litigation, actual or imminent, regarding patent rights, the University may withhold distribution until resolution of the particular matter.

2.4 The University does not act as a fiduciary for any person relating to consideration received under the terms of this policy.

3. ADMINISTRATION

3.1 The President of the University, after consultation with the University Vice President for Technology Development and appropriate campus officials, shall determine the disposition of University discoveries and inventions described in paragraph 1.1 as deemed prudent and consistent with the University's mission to ultimately convey the benefits of its research to the public for the general welfare of the State and Nation. In determining the proper disposition of University discoveries and inventions, the University President shall consult as necessary with scientific and/or technical and/or business subject matter experts in fields appropriate to the discovery or invention under consideration. Among other choices, the University President may:

(A) License the discovery and/or invention to third parties to provide for the further development and/or commercialization of the property;

(B) Transfer the discovery and/or invention for commercialization by entering into commission agreements with third parties to identify potential licensees to further develop and commercialize the property;

(C) Transfer rights to the property to a patent service organization to further develop and commercialize the property;

(D) Allow rights (U. S. and foreign) to the discovery or invention to revert back to the Federal agency that funded the development of the discovery;

(E) Transfer rights (U. S. and foreign) to the discoverer(s)/inventor(s) if requested by the discoverer(s)/inventor(s), and the University President determines that the discovery/invention will not be pursued further by the Office of Technology Development.

(1) If Federal funds where used in the development of the discovery/invention, such transfer of rights are subject to a reversionary right in the Federal government as described in 37CFR401.

(2) Such transfer also shall be subject to an irrevocable, non-exclusive, royalty-free, and world-wide right and license in the University to make, use and/or practice the discovery or invention for University education, research and/or service purposes. The University also reserves the right to publish and or present information and data obtained in the research project resulting in the discovery or invention being transferred, assuming such rights do not jeopardize the discoverer's/inventor's patent rights. Faculty, staff and students shall execute any and all documents, as the University deems reasonably necessary to confirm or enforce such reserved right and license.

(3) Such transfer shall be limited to the discovery or invention duly disclosed to the University, in writing, as of the time the transfer is requested by the discoverer/inventor;

(F) Transfer rights to the discovery and/or invention to the person(s) or entity sponsoring the research in the course of which the discovery or invention was made if such action is required under the terms of the research agreement or is required by law; or

(G) Transfer the discovery and/or invention into the public domain through publication of the invention by the discoverer/inventor.

3.2 All transfers of University discoveries or inventions shall be subject to and contingent upon any rights in third parties as may be governed and/or required by, among other things, sponsored research agreements, other third-party contracts, or law.

3.3 The University Vice President for Technology Development shall be responsible for administering the patent affairs of the University in a manner consistent with this Policy. The University Vice President for Technology Development shall cooperate with the appropriate campus officers to establish written policies to be approved by the President and distributed to the faculty, staff and students of the University, governing procedures to be followed in processing discoveries and inventions generated within the University. The Office of Technology Development shall provide information regarding disposition of specific discoveries/inventions to the inventor(s) no later than six (6) months from the date the discovery/invention is marketed by the Office. If the Office of Technology Development is not going to pursue marketing and/or protecting the invention, rights in and to the discovery/invention shall revert to the inventor(s) upon his/her request.

3.4 When it is in the best interest of the University to get its technology into the marketplace, when the longer term opportunity for returns to the University and the State exceed the short term value of not taking equity, then the University President will approve taking equity. As a matter of principle some equity is desirable in all transactions to create the best opportunity for the University and the State of Oklahoma to get a fair return on the technologies transferred from the University to the marketplace.

4. DISCLOSURE

4.1 It is the responsibility of faculty, staff or students of the University of Oklahoma to report all inventions they may develop during their term of employment or registration as a student.

4.2 Any discovery/invention, whether or not patentable, must be reported to the University by filing an Invention Disclosure Form with the appropriate technology development office. Such Invention Disclosure shall provide sufficient information so that the Office of Technology Development, in conjunction with others, can determine its commercial potential and patentability. Although the maintenance of the laboratory notebooks that describe the discovery/invention is the responsibility of the discoverer/inventor, the Office of Technology Development may

require access to such notebooks at any time throughout the prosecution and maintenance stage of patenting the discovery/invention.

5. TERM

The terms of this Patent Policy are a part of any contractual relationship of the University of Oklahoma with any member of the faculty, staff or student body. This Policy, as amended from time to time, shall be deemed to be part of the conditions of employment of every University employee or a part of the conditions of enrollment and attendance of every student at the University. Any licensing revenues received throughout the duration of such license shall be distributed in accordance with the distribution policy in effect at the time of the signing of such license and can only be changed through mutual agreement of the parties receiving portions of such revenue.

6. UNIVERSITY PATENT COMMITTEE

The University shall have a Patent Committee (for each Campus) that shall consider and investigate disputes among administrators, faculty, or staff and shall recommend appropriate solutions to the President. It shall be convened as needed, but not less than three times per academic year. This committee will consist of one student member appointed by the Graduate Student Senate for one year, two staff members, one appointed by the President and one appointed by the Staff Senate, and five faculty members, three appointed by Faculty Senate and one each by the President and The Vice President for Technology Development. All staff and faculty appointments are for three-year terms. This Committee will assist the University Vice President for Technology Development in setting policy and procedures that will be implemented on a daily basis by the Office of Technology Development staff. The Committee will provide a forum for faculty, staff, and students to present any issues such as, but not limited to, revenue sharing, ownership, etc. The Committee will make recommendations to the University Vice President for Technology Development for the handling of these issues. The Director of the respective campus' Office of Technology Development, the respective campus' Vice Presidents for Research, and University Counsel shall serve as ex-officio members of the Committee.

7. USE OF FACILITIES

As outlined in the Oklahoma Technology Transfer Act of 1998, use of the facilities of the University by a business enterprise or private business entity is allowed when that project involves the research or development of a University technology, whether or not the technology is protected pursuant to federal or state law governing intellectual property, the results of which have potential economic and academic value for the University. Such use of University facilities must be on a "space-available" arrangement in which normal University activities are not displaced. The use of such facilities by a business enterprise or private business will be done on a fee-for-service contract and in conjunction with projects where the University has a vested interest in the outcome of the transfer of University technology, through research and development of a discovery/invention for commercialization purposes, scholarly rewards, or furthers the University's educational, research, or public service missions.

The University may take an equity stake in such business enterprises or private businesses in consideration for the use of such facilities and/or the development of University discoveries/inventions which shall be managed in accordance with the University's policies on stock acquisition and management. Any cash revenues received from the sale or trade of such equity stocks shall be distributed as if received as royalty income. If the equity interest is acquired through an exchange of value other than money and the exchange of value is made in connection with the development of technology by the private business enterprise through the use of the facilities or resources or both of an institution within The Oklahoma State System of Higher Education, acquisition of an equity interest shall be permissible through the use of the facilities, premises or assets of an institution within The Oklahoma State System of Higher Education through the use of faculty expertise or student expertise, including the value of time expended by faculty or students upon developing a technology in connection with a private business enterprise or private business entity. No state appropriated monies shall be used or obligated to acquire an ownership interest in a private business enterprise except as authorized by the provisions of this section.

8. BACKGROUND

8.1 A patent is a grant issued by the U. S. Patent and Trademark Office (PTO) that provides the assignee of the patent the right to keep others from practicing or using its patented invention. Patents are issued for inventions that are novel (not published, sold, or utilized for more than one year), useful, and non-obvious to others equally skilled in the art. (In almost all foreign countries, to be patentable, an invention requires complete novelty. In others words, it cannot have been published, used, sold, or bartered publicly prior to the filing of a patent application either in the country itself or in the United States PTO.)

8.2 U. S. Patent Law has maintained the first-to-invent rule. What this means is that the first person to conceive and reduce to practice the invention shall be entitled to the patent. Foreign countries rely on the first-to-file concept in issuing patent rights. In the case of U. S. law, the laboratory notebooks of the discoverer(s)/inventor(s) may be crucial to the overall outcome of to whom the patent is issued. Laboratory notebooks should be bound notebooks where corrections are readily identifiable. The pages of the notebooks should be signed, dated, and witnessed on a daily basis and stored in a secure location. The term of patent applications filed in recent years is twenty years from the date of application. The laboratory notebooks should be maintained at least for that period of time.

TRADEMARKS

A trademark identifies an item of intellectual property or an educational or training service. The University owns all right and title to any trademarks related to any item of intellectual property owned by the University. Any cash revenues received in exchange for the commercial use or sale of such trademark shall be distributed as those cash revenues received for discoveries/inventions.

COPYRIGHT

1. PREFACE

Copyrights are created by the Constitution and the laws of the United States to promote the progress of science and the useful arts by securing for limited times to authors the exclusive rights to their works and writings. The basic objectives of the University's policy concerning copyright include the following:

(A) To maintain the University's academic policy of encouraging research and scholarship as such without regard to potential gain from royalties or other income.
(B) To make copyrightable materials created pursuant to University objectives available in the public interest under conditions that will promote their effective utilization.
(C) To provide adequate incentive and recognition to faculty and staff through proceeds derived from their works.
(D) To stimulate creativity across all media.

2. POLICY

It is the policy of the Board of Regents of the University of Oklahoma that all rights in copyright shall remain with the creator of the work unless the work is created with substantial use of University resources, is specifically assigned or commissioned by the University, is subject to non-University contractual or legal obligations, or is a "work made for hire" as that term is defined by U.S. Copyright Law.

3. OWNERSHIP

3.1 Scholarly/Aesthetic Works.

In keeping with traditional academic practice and policy, ownership of copyrights to works of artistry or scholarship in the creator's professional field such as textbooks, course materials, scholarly papers and articles, software and other computer materials when they are works of artistry or scholarship, novels, poems, paintings, musical compositions or other such works of artistic imagination produced by University employees who have a general

obligation to produce such works where the specific choice, content, course and direction of the effort is determined by the employee without direct assignment or supervision by the University shall reside in the creators and the works shall not be deemed "works made for hire" under this policy unless they are also sponsored/contracted works or specifically assigned by the University. Copyrighted courseware and/or software that are not associated with traditional works as described above shall fall under and are subject to the Patent Policy. The general obligation of faculty to produce scholarly works does not constitute specific assignment. Upon request by the University, the creator(s) will grant University a nonexclusive, free of cost, world wide right and license to exercise all copyright rights in and to the work, except the right to commercially display, use, perform or distribute copies of the work, unless to do so would impair the ability of the creator to have the work published or distributed. If a use of the work by University is reasonably determined by the creator to impair the exercise of such rights, the University shall discontinue the impeding use but otherwise shall remain free to use the work as provided in this Paragraph 3.1. Subject to the approval of the Vice President for Technology Development, the University will assist any University employee wishing to commercially exploit a scholarly/aesthetic work falling under this paragraph, through the Office of Technology Development and its respective campus officers. In such cases, the University will normally own the work and the provisions of the Patent Policy shall apply.

3.2 Personal Works.

Ownership of copyrights to works prepared outside the course and scope of University employment and without the substantial use of University resources (equipment, facilities, services or funds (regardless of source) administered by and/or under the control of the University) shall reside with the creators; provided, the provision of office facilities, limited secretarial assistance, library facilities for which special charges are not normally made or other resources which are made available to the public without charge, shall not be considered substantial use of University resources.

3.3 Sponsored Works.

Ownership of copyrights to works produced by or through the University in the performance of a written agreement between the University and a third-party/sponsor shall be governed in accordance with the agreement. If the agreement is silent in that regard, ownership shall be governed by the other provisions of this policy.

3.4 Commissioned Works.

Ownership of copyrights to works produced for University purposes by persons not employed by the University or by University employees outside their regular University employment (commissioned works) normally shall reside with the University. In all cases, copyright ownership shall be specified in a written agreement approved by University legal counsel signed by the parties. Any commissioned work agreement which provides for ownership by other than the University shall also provide, to the fullest extent possible, that the University will have an irrevocable, free-of-cost, non-exclusive, world-wide license to exercise all copyright rights in and to the work, except the right to commercially display, use, perform or distribute copies of the work unless to do so would impair the ability of the University employee creator to commercially or professionally exploit the work. If a use of the work by University is reasonably determined by the University employee creator to impair the exercise of such rights, the University shall discontinue the impeding use but otherwise shall remain free to use the work as provided in this Paragraph 3.4.

3.5 University Works.

Except as otherwise provided in this Policy, the University shall own all copyrights to works made by University employees in the course and scope of their employment and shall own all copyrights to works made with the substantial use of University resources. Provided, University shall give due regard to the creator's interests in the quality and integrity of the work and where appropriate grant recognition for creation of the work. To the extent consistent with University rights under the U.S. copyright law, nothing herein shall be construed to prevent the creator from using his/her knowledge, expertise, research and creative achievement in other employment.

3.6 Student Works.

Ownership of copyrights to works produced by enrolled students without the use of University funds (other than Student Financial Aid), that are produced outside any University employment and are not sponsored or commissioned works, shall reside with the student creator(s). Provided however, in all cases a student's graduate thesis or dissertation shall be deemed a student work under this policy but as a condition of enrollment and awarding a degree, the University reserves an irrevocable, non-exclusive, free-of-cost and world-wide right to reproduce in any media and distribute to the public, on a non-commercial basis, copies of said theses and dissertations, unless to do so would impair the ability of the creator to commercially or professionally exploit the work. If a use of the work by University is reasonably determined by the creator to impair the exercise of such rights, the University shall discontinue the impeding use but otherwise shall remain free to use the work as provided in this Paragraph 3.6

3.7 Jointly Originated Works.

Ownership of copyrights to jointly originated works shall be determined by separately assessing the category of work of each creator under this Section 3. Rights between joint owners of a copyright shall be determined pursuant to copyright law or by agreement between the owners of the work.

4. REVENUE SHARING

4.1 The University may assign or license its copyrights to others. The University shall share royalty revenue derived from such assignment or license (excepting commissioned works and sponsored research funding) which it receives through copyrights with the creators, as provided for in the Patent Policy above.

4.2 Notwithstanding the above or anything else to the contrary herein, staff employees are not eligible to share revenues received from University owned copyrights where such employees create copyrightable works as a part of their normal responsibilities of University employment. Provided, a staff employee may apply to the appropriate Provost to be treated as a faculty member for purposes of revenue sharing for a work resulting from a specific project upon a showing that his/her duties and responsibilities in that project are, in practical effect, substantially the same as those of a faculty member.

5. ADMINISTRATION

5.1 Release to the Creator. An individual creator of a University owned work may seek transfer of the University owned copyright to him/herself by making written request to the appropriate Provost. If the University decides not to exploit such work, then it may transfer the copyright, by written agreement, to the individual creator to the extent consistent with any applicable third-party agreement or law. Provided, such transfer shall be subject to an irrevocable, non-exclusive, free-of-cost and world-wide license in the University to exercise all rights under the copyright in the work except the right to publicly distribute copies for commercial purposes or such other conditions as may be agreed upon in writing between the individual creator(s) and the Provost, unless to do so would impair the ability of the creator to have the work published or distributed. If a use of the work by the University is reasonably determined by the creator to impair the exercise of such rights as transferred in the agreement, the University shall discontinue the impeding use but otherwise shall remain free to use the work as provided in this Paragraph 5.1.

5.2 Disclosure and Protection. An individual creator of a University owned copyrightable work shall protect the work by placing the following statutory copyright notice on all copies thereof ("Copyright [insert year produced, e.g., 2000], the Board of Regents of the University of Oklahoma."). If the creator believes the work may have commercial value, he/she shall promptly provide written disclosure of the work to the appropriate Provost.

5.3 Legal Compliance-Any work created by a University employee or student, to the best of his/her knowledge and informed belief, shall not infringe on any existing copyright.

5.4 Creators of copyrightable works subject to this policy and the University shall cooperate as reasonably necessary to effect the terms of this policy. For example, if copyright to a work of scholarship vests in the University

by law, the University will, upon request and to the extent consistent with its legal obligations to third parties, promptly execute such documents as will transfer copyright to the faculty creator(s).

5.5 The Provosts, Norman Campus and the Health Sciences Center, shall be responsible for administering the copyright affairs of the University in a manner consistent with this policy. The Provosts shall cooperate in consultation with the Copyright committee on each campus to establish written directives to be approved by the President of the University and distributed to the employees and students of the University, which shall govern the procedures to be followed in processing copyrighted works created within the University.

5.6 The University does not act as a fiduciary for any person concerning consideration received under the terms of this policy.

5.7 The University Vice President for Technology Development may negotiate ownership of copyrighted works with research sponsors when it is in the best interest of the University to do so. Otherwise, all rights are as described above.

5.8 Faculty having rights to copyrighted works prior to employment at the University of Oklahoma should notify the Office of Technology Development of such intellectual property so that ownership to any further development of that same intellectual property at the University of Oklahoma may be established, in a written agreement with the University.

6. CONTRACTUAL TERM

The terms of this copyright policy are a part of any contractual relationship of the University with any member of the faculty, staff or student body. This policy, as amended from time to time, shall be deemed to be a part of the conditions of employment of every University employee and a part of the conditions of enrollment and attendance of every student at the University.

7. RESOLUTION OF CONFLICT

Should disputes arise relative to the ownership of copyright between the creator and the University, the matter will be referred to the Copyright Committee, which will make recommendations to the President for proper resolution of the disputes. Either the University or creator may contact the Provost to arrange to have the Copyright Committee meet to consider such disputes.

8. UNIVERSITY COPYRIGHT COMMITTEE

(A) The University shall have a Copyright Committee for each Campus that shall consider and investigate disputes among administrators, faculty, or staff and shall recommend appropriate solutions to the President. The Committee's responsibilities shall include, but not be limited to, disputes concerning:

1) Ownership of copyright; and
2) Terms of commissions.

(B) The Copyright Committee of each campus shall have as its members:

(1) One member appointed by the President for a four-year term;

(2) One student member appointed by the Graduate Student Senate for one year;

(3) Two staff members, one appointed by the President, one appointed by the Staff Senate, all appointments are for three years; and

(4) Three faculty members with two appointed by the Faculty Senate and one by the President. All appointments are for three-year terms. Tie votes will be settled by chair of Faculty Senate, who shall be an ex-officio member of the committee.

Each member of the Committee shall have one vote. The Committee shall keep its own records, determine its own procedures, and elect its own chair who shall report to the President. The Committee also may review this policy from time to time and may recommend changes to the President.